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Selected Abstracts
on

RADIOPROTECTORS: EXPERIMENTAL STUDIES AND CLINICAL APPLICATIONS

Theodore L. Phillips, M.D.
Consulting Reviewer

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of the National Cancer Institute

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I

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INTRODUCTION

This ONCOLOGY OVERVIEW on radioprotectors includes abstracts selected from the CANCERLIT database referencing articles published mainly from 1980 to mid-1986. The last CANCERLIT update searched for this ONCOLOGY OVERVIEW was June, 1986.

THE STRATEGY USED TO RETRIEVE THESE ABSTRACTS CAN BE REQUESTED FROM THE CIDAC-CCB AND ENTERED ON ANY MEDLARS/MEDLINE TERMINAL SYSTEM TO UPDATE REFERENCES IN THIS AREA.

The scope of this OVERVIEW covers efficacy and toxicologic studies of radioprotectors in humans and experimental systems, the latter including both normal and tumor-bearing hosts. Areas covered include: protection against different forms of radiation, some with fractionated dose schedules; mechanisms of action; pharmacodynamics and metabolism; drug combinations of several radioprotectors or their use with radiosensitizers. Also included are: synthesis and analysis of chemoprotectors and structure-activity studies; food additives and dietary factors. The use of radioprotectors to modify toxic side-effects of chemotherapy is also reviewed.

This Overview was prepared by Anthony J. Girardi, Ph.D., Subject Specialist for the CIDAC for Carcinogenesis and Cancer Biology, Information Ventures, Inc., Philadelphia, PA. Theodore L. Phillips, M.D. of the Department of Radiation Oncology, School of Medicine, University of California/San Francisco was the Consulting Reviewer and wrote the Editorial Commentary.

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EDITORIAL COMMENTARY

The principle that it was possible to chemically protect against ionizing radiation injury was discovered by Harvey Patt in the 1940s (1). Early observations of decreased lethality in frogs with sulfhydryl containing compounds was followed by measurement of effects on wholebody lethality in rodents and the derivation of the concept of dose modification. The most effective compound found in the next decades was cysteamine which yielded protection or dose modification factors as high as 2 for bone marrow death in mice at the maximum tolerated dose.

Early interest and research support was directed to health physics concerns and possible military uses of protectors. Interest in the possible protection against undesired side effects of radiotherapy was dampened by the findings that cysteamine protects tumors and is toxic at the required doses.

In the 1960s, the U.S. Army sponsored an extensive drug screening and synthesis program that identified a large number of active compounds using a 30 day lethality test in the mouse. Some of the most effective and least toxic compounds were thiophosphates. Yuhas and Storer (2), who had been active in the screening program, discovered that the thiophosphate WR-2721 was particularly effective in protecting marrow and that it was also effective in protecting against radiation injury in small intestine and skin. Of particular interest was their finding that WR-2721 did not protect tumors against the effects of radiation. This lead to a reactivation of interest in the possibility of differential protection of normal tissue as compared to tumor (3).

More recent studies have generally confirmed a differential effect that seems to be due to two factors: the decreased protection of hypoxic cells and poor penetration of the very hydrophillic WR-2721 into tumors. Subsequent work has concentrated on the measurement of protection factors in a wide range of normal tissues, the elucidation of the pharmacology and the introduction of the compound into use in humans.

Progress in the use of radioprotectors for occupational or military exposures has been slow. The most effective and least toxic drugs have been useful only by intravenous administration and have induced considerable side effects. A search for orally administered and less toxic compounds continues.

Sulfhydryl compounds have also been found to protect against the effects of alkylating type cytotoxic agents. Laboratory, as well as clinical studies directed toward the use of WR-2721 to reduce toxic effects and allow higher doses in cancer chemotherapy are progressing.

The first section in this OVERVIEW deals with radioprotector studies in humans. WR-2721 is the major agent, but other compounds have been studied, particularly with topical applications. Both radiation and cytotoxic drug protection have been studied and the maximum tolerated dose of WR-2721 evaluated.

A second large section deals with studies of efficacy and toxicity in experimental systems. Interesting new data on liver protection and protection against carcinogenesis are presented. Protection of the parotid gland and oral structures has been extensively studied. WR-2721 has been evaluated in a wide range of tissues, and a number of interesting new compounds have also been studied. Reduced but significant protection has been shown with high LET radiations and with fractioned exposures.

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The mechanism of action of protectors and their effects on cell biology have been extensively explored. Of particular interest are the abstracts that report work on the role of factors influencing the effectiveness of protectors, in particular the influence of oxygen tension. Reports on the side effects of prostaglandins and the immune system on radiation injury are also included.

Early attempts to elucidate the pharmacology of thiophosphate protectors used radiolabels such that the active and inactive forms of the drug could not be distinguished. Studies using HPLC and other assays are now making possible the identificaiton of parent drugs and metabolites.

In another group of abstracts, drug combinations, new analogs and structure-activity studies are presented, as well as additional pharmacologic assays. Since abstracts often cover several topics, the interested reader should scan the whole set to make sure of finding their areas of interest. Finally, there is a large body of abstracts of interest to the investigator in the area of combined cytotoxic chemotherapy and protectors, followed by a series of review articles.

Special attention should be given to the abstracts of a meeting on Chemical Modifiers of Cancer Treatment held in October 1985, at Clearwater Florida. These papers will appear in the July and August 1986 issues of the International Journal of Radiation Oncology, Biology and Physics. They include updates on pharmacology, human phase I trials, chemotherapy protection and interesting papers on intraluminal and intrathecal administration of protectors.

REFERENCES

1. Patt, H.M., Tyree, E.B., Straube, R.L. and Smith, D.E. Cytesine protection against x-irradiation. Science 110:213 1949.
2. Yuhas, J.M. and Storer, J.B. Chemoprotection against three modes of radiation death. Int. J. Radiat. Biol. 15:233 1969.
3. Yuhas, J.M. and Storer, J.B. Differential chemoprotection of normal and malignant tissues. J. Natl. Cancer Institute 42:331 1969.

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ABSTRACTS

I.

EFFICACY AND TOXICOLOGIC STUDIES OF RADIOPROTECTORS IN HUMANS

1. PROTECTION BY WR2721 OF HUMAN BONE MARROW FUNCTION FOLLOWING IRRADIATION (MEETING ABSTRACT)

Constine L, Zagari ..., Rubin P, Kligerman M
Univ. of Rochester Cancer Center, Rochester, NY 14642
Chemical Modifiers of Cancer Treatment, October 20-24, 1985, Clearwater, Florida, abstract 7-24, 1985

Protection by WR2721 of bone marrow from depression following hemi-body irradiation (HBI) was assessed in patients (pts) receiving palliative therapy for widespread symptomatic metastasis on a Phase I/II Radiation Therapy Oncology Group (RTOG) protocol. In animal studies WR2721 has been shown to protect bone marrow (BM) from the suppressive effects of irradiation. A similar action in humans could potentially increase the efficacy of radiation therapy by allowing the safe delivery of higher radiation doses, or alternatively decrease the severity of hematologic toxicity from currently administered doses. Moderate to life-threatening hematologic toxicity has occurred following HBI in pts on previous RTOG studies. In this protocol HBI (600 to 700 cGy) was delivered starting 10 min after WR2721 (600-750 mg/m2) iv infusion. Twenty pts have been entered into this study, and 18 are evaluable for the assessment of hematologic toxicity. All pts had a pre-treatment white blood cell (WBC) count greater than or equal to 3000 and platelet count greater than or equal to 100,000. Twenty-three pts from previous RTOG HBI studies were comparable in terms of radiation dose and hematologic data (WBC and platelet counts in first 2 wk and subsequent mo following irradiation). Pts who had recent chemotherapy, previous HBI, or tumor involving BM were excluded from evaluation. A table compares the radiation doses and frequency of hematologic toxicity in the pt populations. The WBC and platelet count nadir at any time within 6 wk following treatment were used for data analysis, and toxicity was rated according to RTOG criteria. Using chi-square, the difference between the two groups is significant (p less than 0.005) in spite of the higher HBI dose which most WR2721 pts received. This preliminary data supports a protective effect by WR2721 on radiation-induced bone marrow depression in humans. Treating future pts with higher radiation and WR2721 doses may demonstrate an increased effect. Future investigations will also assess this protective effect on BM hematopoietic progenitor cells (granulocyte-macrophage colony forming units) obtained from this pt population.

2. TOXICITY OF WR-2721 ADMINISTERED IN SINGLE AND MULTIPLE DOSES

Kligerman MM, Glover DJ, Turrisi AT, Norfleet AL, Yuhas JM, Coia LR, Simone C, Glick JH, Goodman RL
Department of Radiation Therapy, University of Pennsylvania, Philadelphia.
Int J Radiat Oncol Biol Phys; 10(9):1775-6 1984

Two hundred forty-three patients have received WR-2721 in Phase I-II studies. Separate studies were conducted in which patients with advanced malignancies received WR-2721 before single or multiple doses of radiotherapy or in single doses prior to cyclophosphamide, nitrogen mustard or cisplatinum. Single doses were escalated from 25 to 1330 mg/m2. An Acceptable Tolerated Dose (ATD) of 740 mg/m2 infused in 15 minutes has been established and is currently used in Phase II studies. Significant persistent hypotension (greater than 20 torr systolic) as a dose-limiting toxicity has occurred in 5% of patients in the single dose study. Fifty-five patients have been entered in the multiple dose trial. Dose levels of 340 mg/m2, four times a week for three weeks, and 250 mg/m2, four times a week for six weeks have been reached. There were five idiosynchratic reactions (fever, chills, rash, hypotension), one of which was severe. Some patients withdrew from the multiple dose study because of vomiting after each injection, or fear. No deaths nor any long-term untoward effects were observed. There is no suggestion of tumor protection.

3. WR-2721 PROTECTION OF BONE MARROW DEPRESSION FOLLOWING HEMI-BODY IRRADIATION IN HUMANS (MEETING ABSTRACT)

Constine L, Zagari G, Rubin P, Kligerman M
Rochester, NY
Radiology; 153(P):178 1984

WR2721 has been shown to protect non-human bone marrow from radiation-induced suppression. To evaluate this potential in patients (pts), an RTOG Phase I/II protocol is investigating WR2721 effects on hemibody irradiation (HBI) for the palliation of symptomatic metastasis. Nine pts who received WR2721 doses of 600-750 mg/m2 and HBI doses of 600-700 cGy were evaluable for hematologic toxicity. Sixteen pts from previous RTOG HBI studies were comparable. No pt had pre-treatment low blood counts, recent chemotherapy, previous HBI, or tumor in bone marrow. A table in the text compares the frequency of hematologic toxicity in the first mo following treatment. The data support the protective effect of WR2721 on radiation-induced marrow depressions in humans. (Modified author abstract)

4. [AN EVALUATION OF THE CLINICAL USEFULNESS OF AMIFOSTINE (YM-08310), RADIOPROTECTIVE AGENT. A DOUBLE-BLIND PLACEBO-CONTROLLED STUDY. 1. HEAD AND NECK TUMORS]

Nitbe H, Takahashi I, Mizuhashi N, Miyaishi K, Itoh J, Maehara Y, Nakajima N, Suto H, Sakaino K, Matsuura S, et al
Nippon Gan Chiryo Gakkai Shi; 20(5):984-93 1985

Keywords (NLM): Adenocarcinoma/radiotherapy; Adolescence; Adult; Aged; Carcinoma, Squamous Cell/radiotherapy; Child; Clinical Trials; Double-Blind Method; English Abstract; Ethiofos/*therapeutic use; Female; Head and Neck Neoplasms/*radiotherapy; Human; Male; Middle Age; Mouth Mucosa/radiation effects; Organothiophosphorus Compounds/*therapeutic use; Radiation-Protective Agents/*therapeutic use.

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5. [AN EVALUATION OF THE CLINICAL USEFULNESS OF AMIFOSTINE (YM-08310), RADIOPROTECTIVE AGENT. A DOUBLE- BLIND PLACEBO-CONTROLLED STUDY. 2. ABDOMINAL AND PELVIC TUMORS]

Niibe H. Takahashi I. Miyashi K. Matsuhashi N. Maehara Y. Nakajima N. Suio H. Saito Y. Yamakawa M. Sugiyama S. et al

Nippon Gan Chiryo Gakkai Shi. 20(5):996-1001 1985

Keywords (MeSH): Adult; Aged; Carcinoma, Squamous Cell/radiotherapy; Cervix Neoplasms/*radiotherapy; Clinical Trials; Double-Blind Method; English Abstract; Ethiofos/*therapeutic use; Female; Human; Male; Middle Age; Organothiophosphorus Compounds/*therapeutic use; Ovarian Neoplasms/radiotherapy; Pelvic Neoplasms/*radiotherapy; Radiation-Protective Agents/*therapeutic use.

6. PREVENTION OF RADIATION DAMAGE TO THE BLADDER AND RECTUM USING LOCAL APPLICATION OF DIMETHYL SULFOXIDE

Zharinov GM. Vershinina SF. Dran'kova OI

Med Radiol (Mosk). 30(3):16-8 1985

A method for the prevention of radiation injuries of the urinary bladder and rectum for cervical cancer patients was worked out. It was based on the local application of the radioprotective agent dimethylsulfoxide (DMSO) before a session of interstitial irradiation with the AGAT-B apparatus. Concomitant radiation therapy with DMSO was provided to 22 cervical cancer patients. The control group included 59 patients who received similar treatment without DMSO. The expression of early reactions and late injuries of the rectum and urinary bladder were significantly lower in the DMSO group. A radioprotective DMSO effect with relation to tumor was not found.

7. CLINICAL RADIO-PROTECTIVE ANTI-INFLAMMATORY EFFECTS BY SUPEROXIDE DISMUTASE (ORGOTEIN)

Kaneda T. Akita S. Usami Y. Su P. Oka T. Matsubara K. Obata Y. Kobayashi H. Sakuma S

Nippon Gan Chiryo Gakkai Shi. 19(4):811-9 1984

Keywords (MeSH): Adult; Aged; *Anti-Inflammatory Agents; Carcinoma, Squamous Cell/*radiotherapy; Combined Modality Therapy; English Abstract; Female; Human; Male; Middle Age; Mouth Neoplasms/*radiotherapy; *Radiation-Protective Agents; Superoxide Dismutase/*therapeutic use.

8. HYPOCALCEMIA AND INHIBITION OF PARATHYROID HORMONE SECRETION AFTER ADMINISTRATION OF WR-2721 (A RADIOPROTECTIVE AND CHEMOPROTECTIVE AGENT)

Glover D. Riley L. Carmichael K. Spar B. Glick J. Kligerman M.M. Agus ZS. Slatopolsky E. Attie M. Goldfarb S

Renal-Electrolyte, Endocrine, Section, Hospital of the University of Pennsylvania, Philadelphia.

N Engl J Med. 309(19):1137-41 1983

We investigated the causes of the hypocalcemia associated with WR-2721, an investigational drug that protects normal tissues against the toxic effects of radiation and chemotherapy. Sixteen patients with advanced cancers had serial measurements of serum calcium and other studies of blood chemistry before and after taking the compound. In all 16 patients (18 courses) the mean serum calcium level fell from 2.33 to 1.90 mmol per liter (9.33 to 7.62 mg per deciliter, P less than 0.001) after WR-2721 , and in all 8 patients from whom data were obtained, serum calcium levels remained depressed at 24 hours. In 12 patients, ionized calcium levels dropped from 0.98 to 0.80 mmol per liter (P less than 0.01). Serum magnesium values fell from 0.96 to 0.74 mmol per liter (1.91 to 1.48 mg per deciliter, P less than 0.001). There were no changes in arterial pH or serum phosphate concentrations. In nine patients urinary calcium excretion rose from 3.96 to 10.68 mumol per minute (P less than 0.01) after WR-2721. Despite hypocalcemia, parathyroid hormone levels fell in all subjects. WR-2721 also inhibited the release of parathyroid hormone from bovine parathyroid cells incubated in vitro in low (0.5 mM) concentrations of calcium. We conclude that WR-2721 inhibits the secretion of parathyroid hormone and enhances calciuria, thereby leading to hypocalcemia.

9. CLINICAL TRIALS OF WR-2721 WITH RADIATION THERAPY

Blumberg AL. Nelson DF. Gramkouski M. Glover D. Glick JH. Yuhas JM. Kligerman MM

(c/o Kligerman) Dept. Radiation Therapy, Univ. Pennsylvania Sch. Medicine, 3400 Spruce St., Box 522, Philadelphia, PA. 19104

Int J Radiat Oncol Biol Phys. 8(3/4):561-563 1982

Phase I clinical trials of the radioprotector WR-2721 [S-2-(3-aminopropylamino) ethylphosphorothioic acid] were carried out in 65 patients receiving palliative irradiation. The objective was to determine the maximum tolerated dose (MTD) of the drug given as a single dose or in multiple doses over several weeks. Fifty patients were treated with a single dose ranging from 25-910 mg/m2 iv and 15 received multiple doses of 100 mg/m2, 1-5 fractions per wk or 170 mg/m2, 3-4 fractions per wk. Acute toxicity observed in both groups included nausea, vomiting, hypotension, hypertension, and somnolence. In the single dose trial, all cases of emesis were of sudden onset. Emesis began towards the end of infusion and stopped within 2 hr after the end of infusion. In the multiple dose trial, two cases of emesis occurred several hr after infusion; these symptoms resolved within 48 hr after the drug was discontinued. Two patients undergoing radiotherapy and one chemotherapy, beeing treated with the multiple dose protocol exhibited allergic reactions including rash, hyperthermia, and one case of anaphylactic shock. For the single dose therapy the MTD has not yet been established; 740 mg/m2 appeared to be well tolerated. Only one patient successfully received 910 mg/m2. (5 Refs)

10. CLINICAL STUDY OF RADIOPROTECTIVE EFFECTS OF YM-08310 IN PATIENTS WITH CARCINOMA OF THE CERVIX UTERI

Takahashi M. Abe M. Kawamura T. Iio A. Hamamoto K. Inohara T

Dept. Radiology, Kyoto Univ. Sch. Medicine, Kyoto, Japan

Nippon Igaku Hoshasen Gakkai Zasshi. 42(5):435-442 1982

To assess the radioprotective effect of YM-08310 (S-2-[3-aminopropylamino] ethylphosphorothioic acid, WR-2721) on improvement of subjective and objective symptoms, a controlled trial has been performe d on 60 patients with carcinoma of the cervix uteri initially undergoing radical and postoperative pelvic radiotherapy. At the beginning of radiotherapy patients were divided by turns into two groups with and without the radioprotective drug, ie the YM-group and the control. Doses of 2 mg/kg of the drug (equivalent to 0.2 ml/kg of the solution) and 0.2 ml/kg of the saline solution were injected intravenously with patients in the YM-group and the control respectively 30 minutes before radiotherapy on each treatment day. The result is that there was no improvement in anorexia and/or nausea. The incidence of diarrhea was, however, about 10% lower in the YM-group than in the control. Counts of erythrocytes and amounts of hemoglobin were essentially unchanged in both groups during radiotherapy. As to other peripheral blood cells the counts of thrombocytes, leukocytes, lymphocytes and their subpopulations (T cells and B cells) fell after treatment and remained

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depressed 2 to 3 months and 10 to 14 months following treatment. However, all of them but B cells kept the mean values of cell counts consistently higher in the YM-group than in the control. Especially for those of thrombocytes at 30 Gy and 50 Gy and T cells at 30 Gy there were statistically significant differences between these two groups. On the other hand the mean of B cell counts in both groups varied with a decrease and an increase of the same degrees during the course of radiotherapy and at follow-up. Radioprotective effect of YM-08310 on the tumor tissue was also studied by cytological and histological examinations at 40 Gy. There was no evidence of radioprotective effects on carcinoma of the cervix uteri. (Author abstract) (35 Refs)

11. PHASE I TRIALS OF WR2721 IN COMBINATION WITH RADIATION THERAPY AND WITH THE ALKYLATING AGENTS CYCLOPHOSPHAMIDE AND CIS-PLATINUM

Kligerman M.M, Blumberg AL, Glick JH, Nelson DF, Glover D, Yuhas JM, Amols HI, Goodman RL
Dept. Radiation Therapy, Hosp. Unit., Pennsylvania, 3400 Spruce St., Philadelphia, PA, 19104
Cancer Clin Trials; 4(4):469-474 1981

Three Phase I trials of the radioprotector S-2(3-amiropropylamino) ethylphosphorothioic acid (WR2721) have accessed 60 patients. Study 1 is devised to determine the max tolerated dose (MTD) of a single dose of the protector 15 to 30 min before a single radiation treatment of a size used routinely in palliative management. Study 2 plans to determine the MTD for up to 15 daily doses of the drug over 3 wk during palliative radiotherapy. Also, the multiple-dose study will establish the MTD before palliative irradiation for fewer than five fractions a wk. Study 3 uses the existing single-dose MTD determined in Study 1 as pretreatment 15 to 30 min before cyclophosphamide or cis-platinum. Toxic symptoms include emesis, hypotension, hypertension, somnolence, and sneezing. Only one serious episode of hypotension, considered idiosyncratic, and one instance of moderate to severe vomiting have occured. Forty-one patients have been entered in Study 1 and a dose of 600 mg/m2 has been reached. The next step is to proceed to the planned highest level of 740 mg/m2. Of five patients in the multiple-dose study, one has been given, without toxicity, WR2721 at the level of 100 mg/m2 for 15 fractions over 3 wk. Fourteen patients are accessed to the alkylating agent study. Using protector doses of 450 mg/m2, a cyclophosphamide level of 1500 mg/m2 has been accomplished. However, two of three patients who received 450 mg/m2 of WR2721 before 120 mg/m2 of cis-platinum have shown moderate elevation of the serum creatinine, both of which returned to normal. (Author abstract) (4 Refs)

12. THE VALUE OF PULVO 47 IN THE PREVENTION OF RADIODERMITITIS

Langeron D, Romestaing P, Papillon J
Service de radiotherapie, Centre Leon-Berard, 28, rue Laennec, 69008 Lyon, France
Gaz Med Fr; 89(34):4182-4185 1982

The effectiveness of the topical skin powder Pulvo 47 in the prevention of radiodermatitis was tested on 14 patients (Group A: 11 women, 3 men) receiving radiation therapy. The Pulvo 47 contained magnesium stearate, hexamidine isethionate, and lactose in the proportions of 10:1:100. The powder was administered locally by aerosol, prior to the radiotherapy. Of eight Group A patients with breast cancer, five underwent surgery for limited adenocarcinoma and received adjunctive radiotherapy, while three had mastectomies and adjunctive radiotherapy. Four of the Group A patients received radiotherapy for basal cell carcinoma, and two received radiotherapy for scars remaining from excisions of sarcomas. Thirteen control patients with similar cancers, Group B, did not receive the Pulvo 47. After 16 days of radiation therapy, 11 patients in Group A had no cutaneous reactions whereas only 5 patients in Group B had no reactions; after 32 days of radiation therapy, 4 patients in Group A had no cutaneous reactions, compared with 3 patients in Group B. At 1 mo following therapy, 9 patients in Group A had normal skin in the irradiated area; at 3 mo, 12 patients. It was suggested that Pulvo 47 improves cutaneous tolerance for irradiation by delaying the appearance of skin reactions and by decreasing the risks of serious skin sequelae following radiotherapy. (4 Refs)

13. THE USE OF AMBIPHILIC DERMATOLOGICAL CREAM AND RADIATION DERMATITIS IN RADIATION THERAPY: A CLINICAL STUDY AT SIRIRAJ HOSPITAL, BANGKOK

Tepmongkol P, Chuthasri S, Rodprasert T, Rattanapol P, Maneenil W
Dept. Radiology, Faculty Medicine, Siriraj Hosp., Mahidol Univ., Bangkok 7, Thailand
J Med Assoc Thai; 64(7):328-332 1981

The radioprotective effect of ambiphilic dermatological cream was evaluated in 25 patients undergoing megavolt (MV) radiotherapy for head and neck cancer and in 25 patients undergoing kilovolt (KV) radiotherapy for breast cancer. The patients received local applications of the cream (in the morning, before irradiation, and in the evening) on the left side (head and neck cancer patients) and on the medial part of the chest wall (breast cancer patients). Moderate to severe skin itching and paresthesia on the side receiving cream application was observed in 0% of patients subjected to MV radiotherapy and in 12% of patients subjected to KV radiotherapy; incidence of itching and paresthesia on the control (nontreated) side was 4% and 32%, respectively. (9 Refs)

14. MEXAMINE EFFICACY IN CANCER PATIENTS UNDERGOING RADIOTHERAPY

Klimenko AA, Karlashenko NI
Res. Roentgenoradiological Inst., Moscow, USSR
Med Radiol (Mosk); 26(5):27-29 1981

The efficacy of radioprotector mexamine was evaluated in 144 patients with esophageal or urinary bladder carcinoma. All patients received distant gamma therapy (180-250 rads/day, 5x/wk, total dose 4,000-8,000 rads). Of 144 patients, 65 (Group I) received mexamine (50 mg, po, 30 min prior to irradiation) and 79 received radiotherapy alone (Group II). The incidence and severity of radiation reactions were similar in both groups. Tumor regression was recorded in 36% of the patients in Group I and in 42.5% of the patients in Group II. Duration of survival in Group I was similar to that in Group II. (18 Refs)

15. CLINICAL EXPERIENCES OF CHEMICAL RADIATION PROTECTION IN TUMOR RADIOTHERAPY IN JAPAN

Tanaka Y, Sugahara T
Tenri Hosp., Tenri, Japan
Radiation Sensitizers: Their Use in the Clinical Management of Cancer. Brady LW, ed. New York, Masson Publishing USA, Inc., Cancer Management, Vol. 5, 521 pp., 1980.

Clinical study of radioprotectors is described. The relationship between iv WR-2721 dose and toxicity was examined in patients. No toxicity was observed below 1.0 mg/kg/day. Side effects were transient, not severe, and usually began during wk 1 post-irradiation. At 30 min and 24 hr after iv administration of 100 mg/kg 14C-WR-2721 to rats, the highest

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organ concentration of labeled WR-2721 was in the salivary gland. Seven groups of mice received WR-2721 (450 mg/kg, ip) 30 min before single fraction irradiation (1,900-3,000 rads). Non-drug-treated mice received 1,500-2,800 rads. Death after oral radiation occurred in nontreated groups at 2,100 rads and in WR-2721-treated groups at 3,000 rads. When WR-2721 was used for the treatment of head and neck tumors, the most serious side effect was mucositis of the oral cavity. (12 Refs)

16. PHASE I CLINICAL STUDIES WITH WR-2721

Kligerman MM, Shaw MT, Slavik M, Yuhas JM
Cancer Res. and Treatment Center, Univ. New Mexico, 900 Camino de Salud, N.E., Albuquerque, NM, 87131
Cancer Clin Trials, 3(3):217-221 1980

Patients in remission following radiotherapy were given S-2-(3-aminopropylamino)-ethylphosphorothioic acid (WR-2721); a dose escalation schedule was used, with a starting dose of 25 mg/meter squared (m2) and increasing to a max of 740 mg/m2. Gastrointestinal function and blood pressure were monitored in patients receiving up to a dose level of 250 mg/m2. There was no evidence of gastrointestinal toxicity; only two patients showed minimal transient discomfort. Changes in blood pressure were noted; however, their significance is questionable. Some patients developed a decrease in blood pressure (8-10 mm Hg systolic) at various times after injection. These results suggest that WR-2721 can be administered in doses up to 170 mg/m2, for possible protection against radiation and alkylating agent injury. It is speculated that this dose level could increase the resistance of the bone marrow by 20-40% and could increase the resistance of the kidney to the nephrotoxic effects of weekly doses of cis-platinum by greater than 50%. (7 Refs)

II.

EFFICACY AND TOXICOLOGIC STUDIES OF RADIOPROTECTORS IN EXPERIMENTAL SYSTEMS

A.

Studies in Normal Animals

17. PROTECTION OF ACUTE AND LATE RADIATION DAMAGE OF THE GASTROINTESTINAL TRACT BY WR-2721

Ito H, Meistrich ML, Barkley HT Jr, Thames HD Jr, Milas L
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Int J Radiat Oncol Biol Phys, 12(2):211-9 1986

WR-2721 was investigated for its protective effect against acute and late damage produced by irradiation of the esophagus, small intestine, and colon of mice. The microcolony assay was used to measure the acute response of the small intestine and the colon, and an LD50 assay (within the 28- to 42-day time range) was used to measure acute esophageal damage. A dose of WR-2721 at 400 mg/kg, injected 30 min prior to irradiation, resulted in a protection factor (PF) of 1.6 against radiation damage in these three regions of the gastrointestinal tract. Lethality and histology scores were applied to determine late radiation damage to the rectum, at times ranging from 3 to 15 months after irradiation. Deaths occurred after doses of 20 Gy and above throughout the postirradiation period. WR-2721 increased the survival of mice; the PF calculated from the LD50 values was 1.5. PFs of animal survival did not vary during the observation period. Histological studies showed evidence of ulceration, fibrosis, and vascular changes as late radiation damage. WR-2721 protected against radiation-induced histological damage with a PF of 1.3. There was no qualitative difference between the types of histological damage observed in the group undergoing only irradiation and the group treated with WR-2721. Biochemical measurements of fibrosis by hydroxyproline determination of collagen 16 months after irradiation showed an increase in collagen per milligram wet weight of rectal tissue in all irradiated groups, but no increase in the amount of collagen per 5 mm segment of the rectum. Thus it appears that the apparent fibrosis is a result of atrophy rather than collagen accumulation. We conclude that WR- 2721 is indeed effective at protection against late damage from large single doses of radiation to the rectum as measured histologically and also improves the long-term survival of the mice, although the target cells for this damage are not known.

18. LATE RADIATION INJURY TO THE GASTROINTESTINAL TRACT; PROTECTION WITH WR-2721 (MEETING ABSTRACT)

Ito H, Meistrich ML, Barkley HT Jr, Milas L
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Thirty-third Annual Meeting of the Radiation Research Society, May 5-9, 1985, Los Angeles, California, p. 127, 1985.

Late appearing damage to the rectosigmoid is a serious complication of pelvic radiotherapy. We studied protection against such damage in the mouse with WR-2721. The drug was given at 400 mg/kg, 30 min prior to exposure of a 15 mm segment of rectum adjacent to the anus to gamma radiation. There was progressive radiation induced mortality of mice throughout the 15-mo follow-up period in both the irradiation only and WR-treated groups. At 15 mo the LD50 was 30 Gy in the WR-treated group compared to only 20 Gy in the control group, for a protection factor (PF) of 1.5. Comparison of LD10 yielded a PF of about 1.3 with no significant variation with time. Histological changes (ulceration, fibrosis and vascular damage) were observed at late times after irradiation; the PF for WR-2721 was about 1.3 for histological damage at 11 mo after irradiation. There was, however, no increase in the amount of collagen (measured as hydroxyproline) per 5 mm length of rectum in irradiated mice, but there was an increase in collagen per mg wet wt of tissue at 16 mo post-irradiation. Thus, fibrosis is more likely a result of tissue atrophy rather than collagen accumulation. The PF's obtained with WR-2721 for early radiation damage to other parts of the gastrointestinal tract were 1.5 for colon, 1.6 for jejunum and 1.6 for esophagus. Thus, WR-2721 can protect the gastrointestinal tract against both early and late damage from high single doses of radiation.

19. PROTECTION AGAINST COLONIC RADIATION INJURY IN RATS BY INTRACOLONIC WR2721 (MEETING ABSTRACT)

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Chemical Modifiers of Cancer Treatment, October 20-24, 1985, Clearwater, Florida, abstract 7-12, 1985.

Phase I testing in humans of the phosphothioate radioprotector, WR2721, has not revealed any long term toxicity, but IV dosages are limited by nausea and vomiting to levels below that shown to protect normal tissues from radiation in laboratory animals. The topical administration of WR2721 was studied to investigate if radioprotection of the colon could be provided without systemic absorption. Under anesthesia, the colon from a male Sprague-Dawley rat was exteriorized. Ligatures were placed around the colon to provide a 2 cm seg-

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ment isolated in vivo with an intact vasculature. A test solution (0.3 ml of WR2721 or 0.15 M NaCl) was then injected into the isolated colonic segment and after a predetermined period of time, the rat was irradiated with 60Co at a dose rate of 125 cGy/min. When rats treated with 45 mg of WR2721 60 min prior to irradiation were compared to those receiving an equivalent dose of saline, a DMF of 1.8 was observed. When the radiation dose and interval from injection to irradiation were fixed at 20 Gy and 60 min respectively, progressively increasing the dose of WR2721 provided significantly greater protection which plateaued at a dose of 15 mg. Irradiation with 20 Gy after each rat received 45 mg of WR2721 showed that intervals from drug injection to irradiation of between 30 and 90 min provided statistically equivalent protection. If the drug was injected less than 30 min before irradiation there was a significant decline in crypt survival. These studies demonstrate that intracolonic administration of WR2721 provides radioprotection of the rat colon similar to that found for other murine normal tissues with ip dosing.

20. PROTECTION OF THE LOW DOSE REGION OF THE SURVIVAL CURVE BY WR-2721 (MEETING ABSTRACT)

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Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-11, 1985.

The ability of WR-2721 to protect after small doses of radiation has been tested in two tissues, jejunum and bone marrow. Groups of mice were exposed to single or fractionated doses of radiation either alone or with the radioprotector WR-2721 given 30 min before each fraction. In all experiments irradiation was given to the whole body. The assays of damage for the jejunum and the bone marrow were the microcolony assay and the exogenous spleen colony assay respectively. The resultant survival curve for each tissue was fitted by linear regression analysis and PFs calculated by the methods of Pike and Alper or Thames and Rasmussen. Although protection of both the bone marrow and the jejunum was significantly less after fractionated doses of radiation, significant protection of both tissues was afforded in the low dose range, PF = 1.2 at doses per fraction between 100 and 200 cGy. Analysis of the jejunum data by the LQ model of survival showed that beta was modified by 50% and that alpha too was modified but by only 20%. These data suggest then that the protection factor will be dependent on the alpha/beta ratio of the tissue and will be higher for late effects tissues than for acute effects tissues. The dose than at which minimal protection will be obtained will be determined by the initial portion of the survival curve (alpha). Defined as the 'flexure' dose by Tucker and Thames, this dose is approx 10% of the alpha/beta ratio for the tissue. Thus, late responding normal tissues would be expected to have similar flexure doses than acute responding normal tissues. In terms of protection the lowest protection will occur after higher doses in acute than late effects tissues and late normal tissue responses should be protected more than acute responses within the dose per fraction range of 50 to 200 cGy. If tumors respond like acute effects tissues, these data suggest that late responding normal tissues will be protected more than tumors within the clinical dose range.

21. [DISTURBANCES OF INTESTINAL MOTOR FUNCTION POST-IRRADIATION: PROTECTION BY WR-2721 AND ITS MECHANISM]

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Zhonghua Fangshe Yixue Yu Fanghu Zazhi; 4(3):22-4, 78 1984

Intraperitoneal injection of radioprotector WR-2721 (250 mg/kg) in rats 30 minutes before 800 rad whole body gamma-irradiation significantly the symptoms and incidence of diarrhea, changes in intestinal weight, and spontaneous contraction and contractile response of small intestine to acetylcholine and nicotine at 3rd day after irradiation. This indicates that WR-2721 can improve the functional disturbance of the intestine in irradiated animals. The mechanism of protective effect of WR-2721 involves the blocking action of intrinsic parasympathetic ganglion of small intestine. The blocking strength of WR-2721 is about half of that of hexamethonium.

22. RADIOPROTECTOR ADMINISTRATION EXERTS OPPOSITE EFFECTS ON THE INDUCTION OF ALTERED HEPATOCYTE FOCI IN MALE AND FEMALE RATS BY COMBINED DIETHYLNITROSAMINE (DEN) AND GAMMA RADIATION (GAMMA) (MEETING ABSTRACT)

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Proc Annu Meet Am Assoc Cancer Res; 27:72 1986

To extend our previous observations regarding the phenotype-specific synergistic induction of altered hepatocyte foci by combined DEN-gamma treatment, we histochemically examined the livers of 150-day-old rats that had been treated neonatally with single doses of gamma (75 or 150 rad, whole body) and intraperitoneally injected DEN (15 mcg/g body wt) and radioprotector [S-2-(3-aminopropylamino)ethylphosphorothioic acid (WR2721, WR), 100 ug/g body wt], with the treatments given separately or in combination. Three focus phenotypes, showing the gammaglutamyltranspeptidase (GGT) and/or the iron exclusion histochemical marker, were quantitated through the use of serial frozen sectioning techniques and computer-assisted image analysis. As reported earlier, in both sexes combined DEN and gamma treatments synergistically increased the frequencies of foci showing only the GGT marker. In females, the addition of WR to this treatment combination reduced the yield of these foci to the level produced by DEN alone. Combining the WR with the DEN and gamma treatments in males substantially increased the yield of GGT foci over that produced by the DEN-gamma treatment; WR alone did not induce foci. Foci showing only iron exclusion were generally decreased in frequency by the DEN-gamma-WR combination, whereas the foci showing both markers were generally unaffected. The results indicate that WR2721 can influence the production of aberrant hepatocyte phenotypes in a sex-dependent manner.

23. PROTECTIVE EFFECT OF WR2721 AGAINST THE INDUCTION OF ALTERED HEPATOCYTE FOCI IN RATS TREATED ONCE WITH GAMMA IRRADIATION WITHIN ONE DAY AFTER BIRTH (MEETING ABSTRACT)

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Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 104, 1985.

We have investigated the protective effects of WR2721 on the induction by radiation of altered hepatocyte foci in 150-day-old Sprague Dawley rats. One hundred micrograms of

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WR2721 per gram of body wt were administered to selected groups of neonatal animals 30 min prior to the administration of single doses of gamma irradiation (150 or 300 rad). Focus phenotypes, gamma-glutamyltranspeptidase (GGT), and/or the iron exclusion histochemical markers, were quantitated through the use of serial frozen sectioning techniques and computer-assisted image analysis. Radiation was effective in inducing foci formation. Induction was much more effective in female as compared to male rats. WR2721 reduced the frequencies of radiation-induced foci at both radiation doses, with the greatest effect apparent in female rats. The protective effect of WR2721 in this system suggests that this compound and related aminothiols may be useful probes for examining mechanisms of mutagenesis and carcinogenesis induced by radiation or chemicals.

24. PROTECTIVE EFFECT OF S-2-(3-AMINOPROPYLAMINO)ETHYLPHOSPHOROTHIOIC ACID AGAINST INDUCTION OF ALTERED HEPATOCYTE FOCI IN RATS TREATED ONCE WITH GAMMA-RADIATION WITHIN ONE DAY AFTER BIRTH

Grdina DJ, Peraino C, Carnes BA, Hill CK
Division of Biological and Medical Research, Argonne National Laboratory, Illinois 60439.
Cancer Res; 45(11 Pt 1):5379-81 1985

We have investigated the protective effects of S-2-(3-aminopropylamino)-ethylphosphorothioic acid (WR2721) on the induction by radiation of altered hepatocyte foci in 150-day-old Sprague-Dawley rats. WR2721 (100 micrograms/g of body weight) was administered to selected groups of neonatal animals 30 min prior to the administration of single doses of ionizing radiation (150 or 300 rads). Two focus phenotypes, described by the histochemical markers gamma-glutamyltranspeptidase and iron exclusion, were quantitated through the use of serial frozen sectioning techniques and computer-assisted image analysis. Although radiation was capable of inducing foci, induction was much more effective in femal e than in male rats. WR2721, however, reduced the frequencies of radiation-induced foci at both radiation doses, with the protective effect more readily apparent in female animals. The modulation of foci formation by WR2721 in the neonatal rat system suggests that this compound and related aminothiols may be useful probes for examining mechanisms of mutagenesis and carcinogenesis induced by radiation or chemicals.

25. CHEMICAL MODIFICATION OF ADRENAL RESPONSE TO EXTERNAL WHOLE BODY IRRADIATION IN MICE

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Acta Radiol kOn.oll; 24(5):427-31 1985

Adult Swiss albino mice were exposed to whole body gamma irradiation with 1.5, 3.0, 6.0 and 9.0 Gy in the presence or absence of the protective drugs MPG and WR-2721. The changes in the total cell population, pyknotic nuclei and necrotic cells, and binucleate cells were observed at various post-irradiation times. The degree of damage increased with the radiation dose. The number of total cells decreased with a corresponding increase in pyknotic nuclei, necrotic cells and binucleate cells. Both drugs provided protection against radiation injury, and reduced early post-irradiation cell damage and enhanced recovery after sublethal exposures. After higher doses, especially after lethal doses, the drugs became less effective in protecting the tissue.

26. POSSIBLE RENAL RADIOPROTECTION WITH 2-MERCAPTOETHANE SULFONATE SODIUM (MESNA) (MEETING ABSTRACT)

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Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-8, 1985

2-Mercaptoethane sulfonate sodium (MESNa) is a sulfhydryl compound that at physiologic pH dimerizes to a divalent anionic disulfide that distributes in the extracellular compartment only. In the brush border of the renal tubules, reductases transform the dimer to the sulfhydryl monomer. This agent has been used to protect the urothelium from the toxicity of Ifosfamide and other chemotherapeutic agents in humans. A unique assay was developed to measure renal damage due to radiation treatment. Mice were nephrectomized on one side prior to irradiation of the remaining externalized kidney. This method was used to study the possible radioprotective effect of MESNa on the kidney. Two groups of 80 male C3HeB/FeJ mice were treated with various single doses of x-rays in the presence and absence of MESNa. A unilateral nephrectomy was performed after which the mice were observed and weighed for four wk to allow the left kidney to hypertrophy. Intraperitoneal injections of MESNa (1000 mg/kg) and saline were given with choral hydrate anesthesia, one hr prior to radiation. The kidney was surgically externalized through an 8mm incision on the lateral abdominal wall. Animals were placed in a lead shielded box which exposed only the externalized kidney. The control (saline treated) and experimental (MESNa treated) groups received single doses of 15 to 50 gray of 250 kVp x-ray in 5 gray increments. Operative mortality was 10%, independent of the time of kidney externalization. Mice were weighed weekly and monthly blood urea nitrogen tests were performed to test renal function. Survival was monitored. Preliminary results at 5 mo show a minimal advantage among the MESNa treated mice both in terms of mean BUN within each dose group and number of mice with BUN greater than 45. The wt loss fraction of mice was measured against the wt of the mice at the time when the wt of the unirradiated (but otherwise identically treated) mice stabilized. Again, a small advantage was noted for the MESNa treated mice. This was not statistically significant. At 5 mo, only 9 mice have died randomly distributed among the dose groups (3 MESNa treated, 6 saline treated) yielding an LD50 at 5 mo of greater than 5000 rad for this renal radiation technique.

27. MODIFICATION OF THE RADIATION INDUCED BRAIN CAPILLARY DAMAGE: DO RUTOSIDES INCREASE THE RADIOPROTECTION OBTAINED BY CHLORPROMAZINE OR FRACTIONATED IRRADIATION (MEETING ABSTRACT)

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Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-5, 1985.

The cerebral microvasculature of the neonatal rat and its radiation induced petechial hemorrhages were used as an in vivo system for investigating the radiation effects on capillaries and its modifiability by different modalities. In earlier studies of our laboratory radioprotection was obtained by either rutosides, chlorpromazine (CPZ) or fractionated irradiation. The aim of the present work was to study the combination of two radioprotectors. Therefore the radioprotective effect of rutosides was investigated (1) in addition to that of

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CPZ and (2) in addition to that of fractionated irradiation. One day old Sprague-Dawley rats (6-7.5 g) in liters of 10-12 pups were used and divided into 2 groups. Both groups received one modality in common and in addition either a second one or a corresponding sham application. The rats were locally irradiated to their head in a warmed and well aerated plexiglass phantom (200 kVp X-rays, 1 Gy /min, 1 Al, HVL:0.24 mm in Cu. Total dose: 5 Gy). One day following irradiation the brains were removed and put into 4% formaline for the examination of the hemorrhages over the brain hemispheres. The extent of the hemorrhages was evaluated according to a scoring scale ranging from 0 to 6. Rutosides (Venoruton, Zyma) 450 mg/kg and CPZ (Largactil, Specia) 5 mg/kg body wt were applied sc (0.03 ml) 30 min before irradiation. Fractionation: 2 fractions of 2.5 Gy (interval: 3 hr). The results are presented in a table. They show a considerable and statistically very significant (Mann-Whitney U-Test) radioprotection of the capillaries by rutosides in addition to either CPZ or fractionation. The radioprotection factors for the additional rutoside treatment (APF) were not quite as high as that for rutosides alone (1.51). The protection factors of the combined treatment of both rutosides and either CPZ or fractionation would amount to 1.7 or 1.8 if estimated from the protection factors for both the single modality and the additional rutoside treatment. Therefore the combined application of two modalities of no or slight toxicity might be preferable to that of a single radioprotector of high toxicity.

28. RADIOPROTECTION IN RAT SPINAL CORD WITH WR2721 FOLLOWING INTRAVENTRICULAR INJECTION (MEETING ABSTRACT)

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Chemical Modifiers of Cancer Treatment, October 20-24, 1985, Clearwater, Florida, abstract 7-14, 1985.

This investigation assesses whether CNS tissue is protected by WR2721 from Cs-137 irradiation. Under ketamine anesthesia Fischer 344 female rats (150 gm) received injections stereotactically in the right lateral ventricle of 0.33 mg (0.6 X LD50 dose) of WR2721 in 5 ul of phosphate-buffered saline (PBS). Control animals received 5 ul of PBS alone. Forty-five min later the rats' cervical spinal cords were treated with Cs-137 irradiation via opposing lateral ports. Except for the cervical spine and structures dorsal to it the remainder of the animals' bodies were shielded with one-inch-thick lead. The animals received 20, 26, 32, or 38 Gy at a dose rate of 1.48 Gy/min. Following irradiation the time in weeks to forelimb and hindlimb paralysis was measured. Statistical significance was assessed by means of the log rank sum test. The to date results are shown in a table. Histological studies from selected spinal cords from symptomatic or sacrificed rats showed petechial hemorrhages, rare microvascular thrombi, and scattered microinfarcts in both gray and white matter regions, but somewhat greater in the white matter. Also, in the white matter columns there were scattered microfoci of demyelination. These data suggest that WR2721 has the capacity to be radioprotective in CNS tissues when it is administered by a route that bypasses the blood-brain barrier.

29. MODIFICATION OF WR-2721 TOXICITY AND RADIOPROTECTION BY AN INHIBITOR OR ALKALINE PHOSPHATASE (MEETING ABSTRACT)

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Dept. of Radiation Therapy, Fox Chase Cancer Center, Philadelphia, PA 19111
Chemical Modifiers of Cancer Treatment, October 20-24, 1985, Clearwater, Florida, abstract 7-18, 1985.

The radioprotective drug, WR-2721 (ie, S-2-(3-aminopropylamino) ethylphosphorothioate), has been shown to be activated in vitro (Shaw, et al, J Liq Chromatography 7:2447-2465, 1984) and in cell cultures (Calabro-Jones, et al, Int J Radiat Biol 47:23-27, 1985) by alkaline phosphatase. Through the use of the alkaline phosphatase inhibitor, levamisole (ie, L(-) 2,3,5,6- tetra-hydro-6-phenylimidazo (2,1-b) thiazole), we are studying the role of alkaline phosphatase in mediating the toxicity and radioprotection of WR-2721 in intact mice. In studying the effect of levamisole on WR-2721 toxicity, we injected (SQ) 40, 75 or 110 mg/kg of levamisole into BALB/c mice 10 min before graded doses of WR-2721 injected IP. We found that 40 mg/kg of levamisole slightly decreased the toxicity of WR-2721 - presumably by partial inhibition of its dephosphorylation to WR-1065 which we find is 3.5X more toxic than WR-2721. The combined lethal toxicity is relatively insensitive to the timing of the levamisole injection relative to the WR-2721 injection except for a 9% increase in WR-2721 toxicity when levamisole is injected 40 min after WR-2721. This timing corresponds to a superposition of the times of toxic death when the drugs are given individually. In studying the effect of levamisole on WR-2721 radioprotection of the gastrointestinal (GI) system, we found that IP injection of 30 mg/kg of levamisole (15 mg/ml) 10 min prior to IP injection of 365 mg/kg of WR-2721 (25 mg/ml) reduced the GI dose reduction factor (DRF) from 1.83 +/- 0.08 to 1.62 +/- 0.14. A portion (33%) of this apparent reduction in protection was due to toxicity of levamisole as demonstrated when levamisole was injected following, rather than before, WR-2721-radiation treatment. Levamisole injection resulted in similar reductions in the radioprotection of the hematopoietic system. To determine whether levamisole did in fact inhibit the dephosphorylation of WR-2721 to WR-1065, we assayed WR-1065 in 2 cm segments of the jejunum using an HPLC electrochemical assay (Shaw, et al, pp 2447-2465). Ten min after injection of WR-2721, we measured 335 +/- 61 nmole/g (N=3) of WR-1065 whereas with SQ injection of levamisole (75 mg/kg) 10 min prior to WR-2721, only 221 +/- 78 nmole/g (N=3) of WR-1065 was measured. We conclude that levamisole is a useful tool for studying and regulating the metabolism, toxicity and radioprotection of WR-2721. (2 Refs)

30. RADIOPROTECTION AGAINST CATARACT FORMATION BY WR-77913 IN GAMMA-IRRADIATED RATS (MEETING ABSTRACT)

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Chemical Modifiers of Cancer Treatment, October 20-24, 1985, Clearwater, Florida, abstract 7-15, 1985.

Radiation-induced cataractogenesis is a potentially serious sequela of tumoricidal doses of radiotherapy for ocular or head and neck tumors. Doses of 12 Gy or greater frequently lead to cataracts. The development of cataracts in rats is not unlikely that observed in humans. Significant protection by WR-77913 against cataract formation was observed during investigation of long term (4-6 mo) rat salivary gland radioprotection by this compound. Male Sprague-Dawley rats (7-9 wk old) received WR-77913 (1160 mg/kg ip) or an equal vol of

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diluent (phosphate-buffered saline, pH=7.24) 15-30 min prior to 15.3 Gy of Cs-137 whole head irradiation. Appropriate sham-irradiated aging controls were included. All non-protected irradiated animals developed dense cataracts throughout the lens at 90-120 days post-irradiation. WR77913 protected rats developed minimal lens opacification. Whole eye and slit lamp photographs documented complete opacification in lenses of non-protected rats, no opacification in control rats and little opacification in WR-77913 treated rats through 200 days post-irradiation. Lens proteins in each group were analyzed by high performance liquid chromatography (HPLC). Lenses from protected and control rats had a small proportion of insoluble protein and large proportion of soluble protein. Insoluble proteins increased and soluble proteins decreased in non-protected lenses. Mol wt composition showed no soluble proteins below 25K daltons in cataractous lenses and high concentrations of protein below 25K daltons in control and protected lenses. In cataractous lenses the protein concentration in the 25-43K dalton range was approx 10% of that found in protected and control lenses. Hydration was substantially higher in cataractous lenses than in protected and control lenses. These results show that WR-77913 protects against lens opacification, protein insolubilization and hydration in lenses of irradiated rats. Biodistribution studies with [S-35]-WR-77913 showed ocular uptake of drug within 15 min after ip injection and it remained through 60 min at a relatively constant concentration. The relative order of drug concentration was: globe greater than vitreous greater than lens. The drug concentration in the lacrimal gland was 6 times that of the whole eye 30 min after injection of labeled drug. These result demonstrate that WR-77913 has a remarkable effect on prevention of radiation-induced cataracts in rats and suggests a potentially significant clinical use for this radioprotective compound.

31. RADIATION PROTECTION OF TISSUES BY MODIFICATION OF THE O2 AFFINITY OF HAEMOGLOBIN IN MICE (MEETING ABSTRACT)

Adams GE, Barnes D, Loutit J, Cole S, Sheldon P, Stratford IJ, Van den Aardweg GJ, Hopewell J

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Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 4-7, 1985.

The substituted benzaldehyde, BW12C, can bind up to the oxy conformation of hemoglobin at a site between the amino termini of the alpha-subunits. This conformationally selective binding produces a left-shift of the oxygen/hemoglobin saturation curve. Consequently, tissues that are normally well oxyg enated would undergo a reduction in the availability of free oxygen. Protection with BW12C against radiation damage to the hemopoietic system in mice receiving whole body radiation has been observed. Mice receiving a single iv dose of 70 mg/kg and irradiated 15 min later with single doses of 250 kV X-rays in the range 7.03 and 13.0 Gy showed a protection dose modification factor of 1.3. In one series of experiments, acute LD50 was raised from 7.5 Gy to 9.7 Gy in drug-treated CBA mice. Blood counts in drug-treated animals showed a more rapid recovery of red cells from the radiation-induced nadir which normally occurs post irradiation. BW12C also protects against radiation-induced loss of epidermal langerhans cells in the mouse foot pad. The dose-modification factor for 70 mg/kg administered 15 min before single doses of X-rays was 1.3. Studies with experimental tumors show a very slight protection against single doses of radiation although the data indicate that the hypoxic fractions in the tumors are increased.

32. COMPARISON OF RADIOPROTECTIVE DRUGS FOR USE WITH LUNG IRRADIATION (MEETING ABSTRACT)

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Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 44, 1985.

Is there a better radioprotector for lungs than WR-2721? We selected eight of the best radioprotective drugs based on our previous studies of radioprotection of the hematopoietic and GI systems and compared them for effectiveness in the protection of the lungs. BALB/c mice received half of the maximum tolerated dose of protector 30 min prior to graded doses of gamma rays to the thorax. The drugs used were WR-2721, WR-638, WR-3689, WR-77913, WR-44923, WR-151327, WR-2529, and diethyldithiocarbamic acid. The progressive damage was assayed in terms of lethality associated with either pneumonitis observed after six mo or pulmonary fibrosis observed after one yr. The LD50 for unprotected controls decreased from 1023 +/- 21 rad at six months to 921 +/- 30 rad at one year. Dose reduction factors (DRF's) for pulmonary fibrosis were 1.49 +/- 0.08, 1.36 +/- 0.07, 1.34 +/- 0.07, 1.34 +/- 0.08, 1.30 +/- 0.08, 1.22 +/- 0.08, 1.16 +/- 0.06, and 1.22 +/- 0.09, respectively, for the drugs listed. The protection provided was greater against late damage (pulmonary fibrosis) than early damage (pneumonitis) as reported previously for WR-2721. Among these drugs, WR-2721 demonstrated the greatest potential for radioprotection of the lungs. It provided a DRF of 1.36 +/- 0.06 against pneumonitis and 1.49 +/- 0.08 against pulmonary fibrosis.

33. COMPARISON OF RADIOPROTECTION EFFECTS OF WR-2721 AND WR-3689 (MEETING ABSTRACT)

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Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 43, 1985.

WR-2721, S-2-(3-aminopropylamino)ethyl phosphorothioic acid, is a very effective radioprotectant, but it is desirable to find a drug that is less toxic and more effective when administered orally. Evidence exists that the less toxic WR-3689, S-2-(3-methylaminopropylamino)ethyl phosphorothioic acid, may be more effective when given orally. In the present study, radioprotective effects of these two compounds administered at equitoxic doses were compared in male CD2F1 mice. The LD50 of cobalt-60 (100 rad/min) more then doubled in mice treated ip before irradiation with either WR-2721 (400 mg/kg) or WR-3689 (450 mg/kg). Treatment po with WR-2721 (700 mg/kg) 1 or 2 hr before irradiation provided better protection than WR-3689 (1000 mg/kg) with survival increased from 850 to 1300 rad. Effects of dietary administration of drugs on post-irradiation survival and on tissue levels of enzymes that protect against oxidative damage were also studied. The effect of drugs on radiation-induced suppression of delayed-type hypersensitivity (Radiat Res 98:438, 1984) was determined. Oral treatment with WR-2721 was slightly more effective than treatment with WR-3689 in protecting cell-mediated immunity. These studies do not indicate that WR-3689 is a more effective oral radioprotectant than WR-2721, but further studies using different drug doses and treatment schedules are necessary. (1 Ref)

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34. RADIOPROTECTIVE PROPERTIES OF DETOXIFIED LIPID A (MEETING ABSTRACT)

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Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 45, 1985.

Endotoxic lipopolysaccharide (LPS) has long been known to possess radioprotective properties. Nevertheless, the toxicity of LPS, or its principal bioactive component, Lipid A, has detracted from its potential use as a radioprotectant. Recently, a relatively non-toxic monophosphoryl Lipid A that retains many of the immunobiological properties of native LPS has been prepared from a polysaccharide-deficient and heptoseless Re mutant strain of S minnesota. We have conducted experiments that evaluated and compared the radioprotective efficiency of native endotoxin, as well as the mono (detoxified) and diphosphoryl (toxic) forms of Lipid A, in both responder (CD2F1 and C3H/HeN) and non-responder (C3H/HeJ) mice. It has been found that the optimal dose for the mono- and diphosphoryl Lipid A are approx the same (800 ug/kg in CD2F1 mice), and that both compounds provide maximum protection when administered 24 hr before exposure to an LD100 dose of cobalt - 60 gamma radiation. Possible mechanisms for the radioprotective action of detoxified Lipid A will be suggested.

35. RADIOPROTECTIVE PROPERTIES OF A FACTOR ISOLATED FROM DEINOCOCCUS RADIODURANS (MEETING ABSTRACT)

Past MR, Jacobs AJ, McPherson EJ, Murray WE Jr, Catravas GN
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Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 45, 1985.

Several organisms are capable of surviving high doses of ionizing radiation. Among the radioresistant organisms are some members of the Deinococcus family of bacteria, including D radiodurans. It has been shown that an extract isolated from D radiodurans confers radioprotection to a more radiosensitive strain of bacteria, E coli. Our laboratory has investigated the radioprotective effects of a low mol wt factor isolated from D radiodurans in mice. Male CD2F1 mice were injected intraperitoneally with the factor 60 min prior to irradiation with 1000 rads (cobalt-60). Irradiated mice treated with 150 mg/kg of the factor showed increased survival and protection against wt loss compared to irradiated controls. When the dosage was increased to approx 375 mg/kg, toxicity of the factor resulted in 30% mortality of the treated mice within 6 days after irradiation. These premature deaths were not observed in control mice. However, despite the toxicity at the higher dose, the 30-day survival of the remaining factor-treated mice was increased compared to controls. Additional research is in progress to determine the chemical composition of this factor, along with further studies of its radioprotective properties.

36. INHIBITION OF RADIATION CARCINOGENESIS IN MICE BY S-2-(3-AMINOPROPYLAMINO)-ETHYLPHOSPHOROTHIOIC ACID

Milas L, Hunter N, Stephens LC, Peters LJ
Division of Radiotherapy, University of Texas M D. Anderson Hospital and Tumor Institute at Houston.
Cancer Res; 44(12 Pt 1):5567-9 1984

We have demonstrated that S-2-(3-aminopropylamino)ethylphosphorothioic acid (WR-2721) given to mice prior to ionizing radiation inhibits development of radiation-induced sarcomas. The right hind legs of C3Hf/Kam mice were exposed to single doses of gamma-rays ranging from 3400 to 5700 rads. Thirty min before irradiation, approximately one-half of the mice were given i.p. injections of WR-2721 (400 mg/kg). Mice were checked for development of radiation-induced tumors within the irradiated tissue of legs from 250 up to 786 days after irradiation. Tumors first appeared in both groups of mice at approximately 300 days after irradiation. Thereafter, the rate of tumor development was slower in mice that received both WR-2721 and leg irradiation. At the end of the observation period, the overall actuarial tumor incidence in these mice was 26%, compared to 87% in mice exposed to radiation only. Since WR-2721 has the ability to protect against radiation carcinogenesis, it may also afford protection against the carcinogenic effect of alkylating agents.

37. TOXICITY STUDIES ON THE RADIOPROTECTIVE AGENT WR-2721 IN CDF1 MICE AND BEAGLE DOGS

Palmer TE, Glaza SM, Dickie BC, Weltman RH, Greenspun KS
Department of Pathology, Hazleton Laboratories America, Inc., Madison, Wisconsin 53704.
Toxicol Pathol; 13(1):58-65 1985

WR-2721, S-2-(3-aminopropylamino)ethylphosphorothioic acid, is used extensively to protect normal cells during the irradiation of neoplastic cells. Dose levels for human radiotherapy are based on results obtained from laboratory animal lethality and toxicity studies. WR-2721 was administered intravenously to CDF1 mice and beagle dogs. Single dose lethality studies in mice showed the average 1/10 of the lethal dose, the median lethal dose and 9/10 the lethal dose to be 508 (1523 mg/m2), 589 (1766 mg/m2), and 682 mg/kg (2047 mg/m2), respectively. The lethal dose for female mice was lower than that for males. The 1/10 lethal dose in mice was slightly toxic to dogs; 1/10 of that dose was nontoxic. The lethal dose for dogs (6000 mg/m2) was higher than that for mice (2000 mg/m2). Clinical signs of toxicosis in the single-dose mouse toxicity study were evident in the 1st week following treatment and declined during the recovery period; signs of toxicosis were transient in dogs. Acute drug-induced pathologic changes included elevated BUN and SGOT levels, lymphoid necrosis, and renal tubular degeneration in mice. These changes were evident in the 1st week following treatment, but had dissipated by study termination. Generalized vascular changes (congestion, hemorrhage, and edema) and renal tubular degeneration occurred in treated dogs that had died or were killed moribund 7 days postinjection. These findings indicate sex-dependent and interspecies variation in the toxicity of WR-2721 with acute, but reversible, pathologic changes.

38. ADVERSE EFFECTS OF RADIOPROTECTOR WR2721

Cairnie AB
Defence Research Establishment Ottawa, Ontario, Canada.
Radiat Res; 94(1):221-6 1983

S-2-(3-Aminopropylamino)ethylphosphorothioic acid (WR2721) has radioprotective properties, but it is also toxic - in man it causes nausea and vomiting. Since radiation also causes nausea and vomiting it is important to know whether WR2721 would increase or decrease the likelihood of nausea and vomiting after radiation. This question was investigated in rats using the phenomenon of aversion to the taste of saccharin, which is readily inducible and is understood to be controlled in rats by the same pathways that control nausea and vomiting in man. The taste aversion was induced by giving 0.2 Gy60Co gamma radiation 30 min after drinking 0.1% saccharin, or WR2721 immediately after the saccharin, or giving both radiation and WR2721. There were appropriate controls. In sham-irradiated rats, WR2721 (40 or 200 mg/kg, but not 8 mg/kg) produced a significant taste aversion.

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When WR2721 (40 or 200 mg/kg) was given immediately after the saccharin to irradiated rats it increased the taste aversion significantly, but it did not have any effect at 8 mg/kg. It was concluded that at doses which were optimal for radioprotection (approximately 200 mg/kg) or lower, WR2721 increased in rats the taste aversion induced by radiation. By inference if conditioned taste aversion is an appropriate paradigm, WR2721 would increase nausea and vomiting in man induced by radiation.

39. ANALYSIS OF THE TOXICITY AND RADIOPROTECTIVE EFFECT OF THE CHEMICAL RADIOPROTECTOR WR 2721 IN DOGS (BEAGLES), PART 2: RADIOPROTECTIVE EFFECT OF WR 2721

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Strahlentherapie; 156(9):655-662 1980

In order to examine the efficacy of the radioprotective agent aminopropylamino-ethylthiophosphate (WR 2721) in larger animals, 43 adult male dogs (beagles) were exposed to gamma rays. The LD50/30 values were determined by probit analysis. The LD50/30 value for unprotected control animals has been found to be around 274 rad, while for animals pretreated with 150 mg WR 2721/kg body wt this value was about 632 rad. Hence the DRF due to WR 2721 is 2.3 ie, the midlethal dose of irradiation for protected animals was 2.3-fold higher compared to control animals. The protective action of WR 2721 was also indicated by lesser post-irradiation decrease of thrombocytes, WBC and lymphocytes and by the quick recovery of bone-marrow. The symptoms of radiation sickness were observed in the protected dogs only after exposure to high doses (650 and 750 rad). All data on clinical-chemical parameters of sera were subjected to variance and discriminant analyses. Based on these clinical data the animals could be classified with 90% certainty into their exposure doses. The discriminant analyses of these data allowed the prediction of whether an experimental animal would die before or after the 10th day postradiation or survive the assault. These clinical data have obvious relevance to the problem of biological dosimetry. (Author abstract) (10 Refs)

40. INVESTIGATIONS WITH BEAGLES ABOUT TOXICITY AND RADIOPROTECTIVE EFFECT OF THE CHEMICAL RADIOPROTECTION SUBSTANCE WR 2721. PART I. TOXICITY OF WR 2721

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Strahlentherapie; 156(7):486-491 1980

The toxicity of the chemical radioprotection substance WR 2721 (S-2-(3-aminopropylamino)ethyl-thiophosphate) was examined in 25 beagles. The study showed that the toxicity of the substance increases as the dose gets higher. Between the doses 200 and 250 mg/kg of body wt, the increase of toxicity was significantly greater than could be expected on the basis of the dose difference. Up to a dose of 200 mg/kg, the authors found no side effects which would have disturbed vital functions, but higher doses led to marked symptoms of intoxication. (Author abstract) (8 Refs)

41. INVESTIGATIONS ON COMBINED INJURIES, 29TH COMMUNICATION. PROTECTIVE EFFECT OF AMINOPROPYLAMINO-ETHYLTHIOPHOSPHATE (WR 2721) IN MICE WITH RADIATION AND COMBINED INJURIES (IRRADIATION AND SKIN WOUND OR BURN)

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Strahlentherapie; 156(8):572-578 1980

Because of the crucial practical importance of combined injuries, investigations of the efficacy of the radioprotective agent aminopropylamino-ethylthiophosphate (WR 2721) were performed on mice which were whole-body x-irradiated and stressed with a second trauma either as an open wound or as burn wounds on the skin. In cases of sole whole-body irradiation, probit analyses of our data yielded the dose reduction factors (DRF) of 2.42 (NMRI-Hannover) and 2.12 (NMRI-Kisslegg). In case of a combination of an open skin wound (SW) with irradiation in mice of the Hannover breed the following dose reduction factors have been obtained: for irradiation + SW 10 min pr the DRF 2.22, for irradiation + SW 2 days pr the DRF 2.30, and for irradiation + SW 8 days pr the DRF 2.29. In cases of combined injuries with two burn wounds (BW) as second trauma in mice of the Kisslegg breed yielded: the DRF 2.01 for irradiation + BW 10 min pr, and the DRF 1.91 for irradiation + BW 2 days pr. The protective effect of WR 2721 is apparently similar in the various groups with combined injuries as compared to the animals exposed to whole-body irradiation only. The mechanisms of action of the sulfur-containing radioprotective agents are discussed. (Author abstract) (16 Refs)

42. RADIOPROTECTION BY WR-2721 OF GAMMA-IRRADIATED RAT PAROTID GLAND: EFFECT ON GLAND WEIGHT AND SECRETION AT 8-10 DAYS POST IRRADIATION

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Int J Radiat Oncol Biol Phys; 10(9):1535-9 1984

Changes in rat parotid salivary gland weight and functional parameters were evaluated at 8 to 10 days post irradiation in WR-2721 protected and non-protected animals following exposure to a single 15.3 Gy dose of Cs-137 radiation to the head. Glandular fluid secretory capacity was assessed by maximum flow rate, total volume of saliva and duration of secretion following pilocarpine stimulation. Protection against radiomucositis was also evaluated indirectly by daily monitoring of food and water intake, body weight and paraoral symptomatology. WR-2721 provided a significant degree of protection for all glandular functional parameters as well as gland weight. Relative protective factors (RPF) were computed for irradiated protected and non-protected animals compared to their sham-irradiated, pair-fed controls. The calculated RPFs were: Gland weight 1.9, maximum flow rate 2.9, volume of saliva 2.1 and duration of secretion 2.1 for a mean 'relative protection' of 2.25. Substantial protection against radiomucositis in protected animals was evident by a progressive gain in body weight and lack of oral signs and symptoms as compared to non-protected animals. Protection against radiomucositis and preservation of residual parotid gland secretory capacity as determined by functional parameters suggests that WR-2721 may be of significant benefit in alleviating oral symptoms and maintaining salivary gland

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function for patients receiving radiotherapy for head and neck tumors.

43. RADIOPROTECTION OF THE RAT PAROTID GLAND BY WR-2721: MORPHOLOGY AT 60 DAYS POST-IRRADIATION

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Dept. Anatomy, Temple Univ. Sch. Medicine, 3420 North Broad St., Philadelphia, PA, 19140
Int J Radiat Oncol Biol Phys; 6(4):431-435 1980

Rats were given ip the radioprotective agent S-2 (3-amino-propylamino)-ethyl phosphorothioate (WR-2721) then after 15-20 min were irradiated (x-rays, 3.2 kilorad, 1 dose) to the right side of the head; 60 days later, the parotid glands were prepared for study. In rats not protected, there was a great reduction in acinar tissue (with remaining acini having excessive and redundant basal laminae), but ducts and blood vessels showed only minor changes. WR-2721-protected glands showed a much lower degree of the same damage. (22 Refs)

44. ISOPROTERENOL IN COMPARISON TO WR-2721 AS A CHEMORADIOPROTECTOR OF THE RAT PAROTID GLAND

Sodicoff M, Conger AD, Pratt NE
Dept. Anatomy, Temple Univ. Sch. Medicine, 3420 N. Broad St., Philadelphia, PA, 19140
Invest Radiol; 14(2):166-170 1979

A comparison was made of the radioprotective abilities of the chemoradioprotector WR-2721, an amino-thiol, and the beta-sympathomimetic secretagogue isoproterenol on the rat parotid gland. Using the dose-response curve of WR-2721 for gland wt as a basis for comparison, isoproterenol was found to offer significant and equal protection during both the acute and the chronic periods. (Author abstract) (19 Refs)

45. RADIOPROTECTION OF ORAL CAVITY STRUCTURES BY WR-2721

King R, King R, Giansanti JS
Dept. Radiology, Div. Radiation Oncology, Univ. California, San Diego, CA, 92103
Int J Radiat Oncol Biol Phys; 4(7/8):643-647 1978

The phosphorothioate, WR-2721, is a potent radioprotector of certain normal tissues and moderately to poorly protective of others. Previously determined high levels of WR-2721 in mouse salivary glands suggested possible radioprotection of these glands from ionizing radiation. Balb/c mice (7-9 wk) were used for the study of the oral radiation death syndrome (LD50/8-10: LD50 of animals in 8-10 days following irradiation of the head). Eight groups of mice received 500 mg/kg ip WR-2721 30 min before single fraction irradiation doses, which ranged from 3,000-3,700 rads, to the head and neck. The mice were scored for lethality 8-10 days following irradiation using the method of Litchfield and Wilcoxon to estimate the 50% lethal effect. Physiological changes of the irradiated salivary glands and the radiation reaction of oral cavity structure and skin were studied in mongrel dogs given 70 mg/kg iv WR-2721 30 min before irradiation with 1,000, 1,500, 2,000 or 2,500 rads delivered as a single fraction to the left half of the head. The flow of saliva from each buccal pouch was determined before treatment and weekly to monthly intervals for a period of 6 mo following irradiation The acute and chronic changes which occurred in the oral cavity and skin were photographed. In untreated mice the LD50/8 10 occurred at 1,600 rads while in treated mice this occurred at 3,354 rads. No significant radioprotection against decreased salivary flow was found. Grade 3 skin reaction, or total hair loss occurred at 2,500 rads in the WR-2721 treated dog and at 1,500 rads for control. Grade 4 reaction or moist desquamation of skin occurred following 3,000 rads in the protected animal and 2,500 rads in the control dog. The oral mucosal reactions were consistently greater in the control animals. Necrosis appeared at the left retromolar trigone 3 mo following 3,000 rads in the drug-treated dog and 2,500 rads in the control dog. These results indicate possible use of WR-2721 as a radioprotective agent of normal epithelial structures of the head and neck. (13 Refs)

46. RADIOPROTECTION BY WR-2721 AGAINST LONG-TERM CHRONIC DAMAGE TO THE RAT PAROTID GLAND

Sodicoff M, Conger AD, Pratt NE, Trepper P
Dept. Anatomy, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Radiat Res; 76(1):172-179 1978

The radioprotective effects of the compound WR-2721 were tested by injecting it (400 mg/kg) into female Sprague-Dawley rats 15-20 min before half-head irradiation (right parotid gland irradiated, left gland shielded) with x-rays (1.6-4.8 kiloR, at 140 R/min). Damage was assessed by determining wt ratios and amylase ratios of the irradiated gland/shielded gland within the same animal. WR-2721 had a protective effect against the acute phase of radiation damage which appears during wk 1 after irradiation, but recovery occurred in the presence or absence of the compound. During the chronic phase, which appeared 60-90 days postirradiation, protection due to WR-2721 was evidenced by dose modification factors of 2.3, 3.2, and 2.0 for gland wt, amylase, and total gland amylase, respectively. The results suggest the usefulness of WR-2721 in reducing xerostomia and its attendant complications in patients undergoing radiotherapy for tumors that involve radiation of the mouth. (7 Refs)

47. SHORT-TERM RADIOPROTECTIVE EFFECTS OF WR-2721 ON THE RAT PAROTID GLANDS

Sodicoff M, Conger AD, Trepper P, Pratt NE
Dept. Anatomy, Temple Univ. Sch. Medicine, 3420 North Broad St., Philadelphia, PA, 19140
Radiat Res; 75(2):317-326 1978

The radioprotective effects of WR-2721 [S-2-(3-aminopropylamino) ethylphosphorotioic acid] on rat parotid gland following x-irradiation are described. Female Sprague-Dawley albino rats were irradiated with 1.6, 3.2 and 6.4 kiloR of acute x-rays to one-half of the head. WR-2721 was given 15 to 20 min prior to irradiation. Gland wt and amylase concentrations were determined as indicators of the direct effect of irradiation on the gland. Gland wt, amylase concentration and within animal effect (irradiated gland to shielded gland) were determined on days 1 to 9 for animals at the three exposure levels, with and without WR-2721. Analysis of the dose-response curves of nonprotected vs protected animals gave dose modification factors of 2.5 for gland wt, 1.7 for amylase concentration, and 1.8 for total gland amylase. This indicates that WR-2721 is effective in protecting normal tissues of the salivary gland from the effects of radiation. (15 Refs)

48. MORPHOLOGICAL EFFECTS OF WR-2721 ON THE RAT PAROTID ACINAR CELL

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Temple Univ. Sch. Medicine, 3420 North Broad St., Philadelphia, PA, 19140
Radiat Res; 75(2):327-335 1978

The effects of WR-2721 [S-2-(3-aminopropylamino) ethyl phosphorothioic acid], a radioprotective compound, on the ultrastructure of the rat parotid acinar cell were examined to eludicate the mechanism of chemoprotection in the absence of any radiation. Twelve female Sprague-Dawley rats were

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fasted for 18 hr and then injected ip with 400 mg/kg of WR-2721 and sacrificed for EM studies 20 and 60 min followinig injection. There were no significant changes in either the gland wt or amylase concentration at either 20 or 60 min. However, morphological studies indicated that WR-2721 caused secretion to continue in the parotid gland. There was a variable increase in lysosomal elements, although all the other cellular organelles appeared normal. The presence of lysosomal products may not indicate toxicity or mechanical damage, but may be part of the active secretory process. The observed ultrastructure in WR-2721 parotid acinar cells could reflect hypoxic changes. Hypoxia has been hypothesized as the mechanism in chemoprotection. Overall, WR-2721 does not cause overall organelle distortion, as has been found in other radioprotective agents. (33 Refs)

49. EVALUATION OF DIETHYLDITHIOCARBAMATE AS A RADIOPROTECTOR OF BONE MARROW

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Department of Radiation Oncology, Cross Cancer Institute, Edmonton, Alberta, Canada.
Int J Radiat Oncol Biol Phys; 10(9):1569-73 1984

The radioprotective action of DDC on normal hematopoietic tissue in mice was evaluated. An increase in CFU-S and CFU-GM in DDC treated unirradiated control mice was consistently observed. When post-irradiation survival of CFU-S and CFU-GM from DDC treated animals was normalized to account for this observed increase, protection factors ranging from 0.9 to 1.6 were observed. These protection factors are significantly lower than those reported by others. Maximum radioprotection was observed when irradiations were performed 15 to 30 min after DDC treatment; maximum increase in GFU-GM occurred within one to two hr following treatment. The increase in CFU-GM is analogous to that observed in animals treated with endotoxin, a non-thiol radioprotector. When C3H/HeJ mice, which are genetically incapable of responding to endotoxin, were challenged with DDC, an average CFU-GM increase of 1.7 times was observed, suggesting that the stimulatory effects of DDC were not due to endotoxin contamination. DDC was administered daily for three days before irradiation and little or no increase in CFU-GM and no radioprotection was observed, suggesting that the marrow can become refractory to DDC. When WR-2721 was tested in similar studies, a dose-modifying radioprotection was observed, with no significant nonspecific stimulation of hematopoietic cells.

50. THE EFFECT OF CYSTAMINE PROTECTION ON POSTIRRADIATION RECOVERY OF HEMOPOIESIS AS MEASURED BY 125I-IODODEOXYURIDINE UPTAKE IN BONE MARROW, SPLEEN AND THYMUS OF MICE

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Radiobiol Radiother (Berl); 23(4):433-441 1982

The possibilities of using proliferation characteristics of hemopoietic organs in irradiated mice for quantitative evaluation of cystamine radioprotection were examined. Cell proliferation in the femoral bone marrow, spleen, and thymus was assayed using 125I-iododeoxyuridine (125I-UdR) technique. 125I-UdR indicated radioprotective action only at early postirradiation intervals in the bone marrow exhibiting an effective cellular repopulation. (28 Refs)

51. SODIUM HYDROGEN-S-(3-AMINO-2-HYDROXYLPROPYL) PHOSPHOROTHIOTATE (WR-77913): TOXICITY AND BONE MARROW RADIOPROTECTION

Mendiondo OA, Connor AM, Grigsby P
Dept. Radiation Medicine, Univ. Kentucky Medical Center, 800 Rose St., Lexington, KY, 40536-0084
Int J Radiat Oncol Biol Phys; 8(3/4):553-555 1982

Toxicity and radioprotective effects of sodium hydrogen-S-(3-amino-2-hydroxypropyl) phosphorothioate (WR-77913) were compared with those of S-2-(3-aminopropylamino)ethyl phosphorothioic acid (WR-2721) in 12-wk-old female BALB/c mice when given ip 30 min before whole body irradiation. WR-77913 warrants further study because of its low toxicity, non-additive toxicity with WR-2721, less toxicity in combination with misonidazole, and adequate bone marrow protection at 25% of the max tolerable dose. (9 Refs)

52. PROTECTION OF BONE MARROW AND GASTROINTESTINAL TRACT AS CRITERIA FOR COMPARATIVE EFFICACY OF RADIOPROTECTIVE AGENTS

Piatovskaia NN, Brumberg IE
S. M. Kirov Military-Medical Acad., Leningrad, USSR
Radiobiologiia; 22(2):183-186 1982

Comparative radioprotective efficacy of 4-aminobenzo-2,1,3-thiadiazol (ABT) and cystamine (CA) was studied in male random-bred and BALB/c mice irradiated with 750 and 1,000 rads. ABT and CA were given ip (225 and 50 mg/kg, respectively) or po (400 and 75 mg/kg, respectively). The survival rate during 7-30 days after irradiation was 81% for mice treated with CA and 57% for mice treated with ABT. CA prevented development of the intestinal syndrome in 76% of the animals, compared with 8-17% protection after ABT administration. (14 Refs)

53. RADIOPROTECTIVE EFFICACY OF POLYRIBOINOSINIC ACID-POLYRIBOCYTIDYLIC ACID (POLY I-POLY C). COMMUNICATION I. EFFECT OF POLY I-POLY C ON HEMATOPOIETIC SYSTEM AND SURVIVAL OF IRRADIATED ANIMALS

Zbukova NA, Palyga GF, Maksimenko AA
Res. Inst. Medical Radiology, Obninsk, USSR
Radiobiologiia; 21(3):358-362 1981

The radioprotective effect of polyriboinosinic acid-polyribocytidylic acid (poly I-poly C) was studied in (CBAxC57Bl)F1 mice. Animals were subjected to a whole body irradiation with 400-950 rads; 2 days prior to irradiation mice received single ip injection of poly I-poly C (2.5 mg/kg). Poly I-poly C increased the survival rate of mice irradiated with 750 rads. The radioprotective effect of poly I-poly C on hematopoiesis (WBC and myelokaryocyte count, the frequency of chromosome aberrations in the bone marrow cells) was recorded only in animals irradiated with 400-650 rads. (18 Refs)

54. RADIOPROTECTIVE EFFECTS OF DEXTRAN SULPHATE IN MICE

Vacek A, Palyga GF, Bartonickova A, Zbukova NA, Rotkovska D
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Strahlentherapie; 157(10):692-695 1981

Influence of a single ip infection of dextran sulfate on radiosensitivity of mice was investigated. The administration of dextran sulfate 24, 48 and 72 hours prior to irradiation increased formation of endogenous colonies of the hemopoietic tissue on the surface of the spleen. DRF calculated from an equieffective exposure for five colonies was 1.96 when dextran sulfate was administered 24 hours before irradiation, and 2.25 when dextran sulfate was administered 72 hours

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before irradiation. The radioprotective effects of dextran sulfate were manifested also in the survival of animals exposed to lethal doses of short-termed as well as long-termed gamma radiation. (Author abstract) (18 Refs)

55. DRUG PRETREATMENT ENHANCES RECOVERY OF IRRADIATED MOUSE BONE MARROW

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Appl Radiol; 10(4):97-100 1981

Research on the effects of treating mice or humans with drugs such as cytosine arabinoside, L-cysteine, and cyclophosphamide prior to radiotherapy was discussed. It was shown that pretreatment with cytosine arabinoside resulted in enhanced postirradiation hemopoietic stem cell recovery from radiation-induced depletion of bone marrow and that bone marrow cells were not the only normal tissue which can be spared by combination chemo- and radiotherapy. (13 Refs)

56. SURVIVAL OF BONE MARROW-ENGRAFTED MICE SUBSEQUENT OF PROTECTION FROM LETHAL RADIATION BY WR2721

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Radiat Res; 82(1):215-219 1980

The value for combining bone marrow grafts with the use of the radioprotective chemical WR2721, was investigated in mice exposed to whole-body radiation from a 60Co source. The data were analyzed in terms of the LD50/30, the radiation dose which causes death in 50% of the animals within 30 days. In mice not protected with WR2721 and without bone marrow grafts, the LD50/30 was 824 +-8 rad. In mice that received WR2721 before radiation exposure but without bone marrow grafts, the LD50/30 was 1,342 +-27 rad. In mice that received bone marrow grafts from healthy, syngeneic mice, but did not receive W2721, the LD50/30 was 1,181 +-33 rad. In mice that received bone marrow grafts from healthy, syngeneic mice, and were also given WR2721 prior to irradiation, the LD50/30 was 1,608 +-33 rad. Each of the four values of LD50/30 are significantly different at the 1% level, from each of the other three values. The results demonstrate the effectiveness of the combination of bone marrow grafts and radiochemical protection. (15 Refs)

57. RADIATION PROTECTION OF PRONORMOBLASTS AND NORMOBLASTS BY 2-MERCAPTOPROPIONYLGI YCINE (MPG)

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Radiation Biology Lab., Dept. Zoology, Univ. Rajasthan, Jaipur-302004, India

Experientia; 36(1):448-449 1980

The pronormoblasts and normoblasts in Swiss albino mice were found to be very sensitive to radiation and their percentage was reduced drastically after exposure to gamma-rays. The degree of damage increased with increase in radiation dose. MPG reduced the initial damage and brought about an early and fast recovery. It is concluded that the drug protects the stem cells and thereby reduces the depletion of the regenerating pool which causes a more efficient and accelerated recovery. (Author abstract) (9 Refs)

58. EARLY RESULTS OF THE SCREENING PROGRAM FOR RADIOPROTECTORS

Brown DQ, Pittock JW, Rubinstein JS

Fox Chase Cancer Center, 7701 Burholm Ave., Philadelphia, PA, 19111

Int J Radiat Oncol Biol Phys; 8(3/4):565-570 1982

A screening program for radioprotectors has screened 20 compounds thus far. Most of the compounds provided good protection of the mouse hematopoietic system as indicated by 30-day survival after radiation at a dose lethal to 100% of the animals at 30 days. Hematopoietic dose reduction factors (DRF) as high as 2.3 were determined with administration of radioprotector doses of one half the max tolerated dose. WR-2721 was the most protective compound, while four other radioprotectors gave DRF greater than 1.8. (7 Refs)

59. SOME RADIOBIOLOGICAL EFFECTS IN SOMATIC CELLS OF MICE EXPOSED TO DEUTERONS AND TREATED WITH ADETURON

Tenchova VB, Topalova STs, Ryzhov NI, Panteev TP, Minkova MI

Res. Inst. Roentgenology and Radiobiology, Medical Acad. People's Republic Bulgaria, Sophia, Bulgaria

Radiobiologiia; 20(6):919-921 1980

Biological effects of deuteron irradiation (4.2 giga-electron-volt/ nucleon) and modification of these effects by adeturon (300 mg/kg animal body wt, ip, 15 min before irradiation in the dose of 201 rads) were studied in male CBA x C57Bl/6 F1 mice. Changes in the concentration of nucleic acids (NA) in the leukocytic blood mass and a micronuclear test of chromosomal damages in bone marrow cells, as registered 24 hr after irradiation (27-201 rads), served as criteria. Deuteron irradiation caused a progressive diminution of NA level in blood and an increased occurrence of micronuclei in karyocytes as function of radiation dose. The findings indicated possible existence of two thresholds of resistance to the effect of deuteron irradiation, and thus, existence of cell populations with various radiosensitivity. Prophylactic administration of adeturon reduced radiation-induced damage. (4 Refs)

60. RADIOPROTECTIVE EFFECT OF A PROTEIN FREE PARATHYROID EXTRACT ON THE MITOTIC INDEX OF RAT BONE MARROW CELLS

Feuer L, Ormai S

Chinoin Pharmaceutical and Chemical Works Ltd., H-1325 Budapest, Hungary

Experientia; 35(8):1091-1092 1979

The protective efficacy of an orally administered bovine protein-free parathyroid extract (PF-PTE) was studied on rat bone marrow cells in vivo with the mitotic index after 850 R irradiation. A remarkable decrease was found in the mitotic activity of bone marrow cells after irradiation in the non-protected animals. However, in the animals treated with PF-PTE after irradiation, a significantly smaller decrease and a faster recovery was found in the mitotic activity of the bone marrow cells. (Author abstract) (3 Refs)

61. MODIFICATION OF RADIATION-INDUCED SPLEEN WEIGHT CHANGES IN MICE BY 2-MERCAPTOPROPIONYLGLYCINE

Saini MR, Devi PU

Radiation Biology Lab., Dept. Zoology, Univ. Rajasthan, Jaipur-392994, India

Experientia; 35(12):1628-1629 1979

It was found that the 2-mercaptopropionylglycine (MPG) partially protects the spleen against wt loss due to radiation, and exaggerates the compensatory reaction in the tissue during recovery. It is also concluded that MPG protects the

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stem cells in the spleen, which helps to restore the peripheral blood by extramedullary erythropoiesis. (Author abstract) (15 Refs)

62. PROTECTION OF INTESTINAL DAMAGE BY PRETREATMENT WITH CYTARABINE (CYTOSINE ARABINOSIDE)

Phelps TA, Blackett NM
Block F., Radiotherapy Res., Inst. Cancer Res., Clifton Ave., Belmont, Surrey, England
Int J Radiat Oncol Biol Phys; 5(9):1617-1620 1979

The effect of pretreatment with cytosine arabinoside (ara-C) on the radioresistance of intestinal epithelial stem cells was studied. Mice were subjected to split-course irradiation and were inoculated ip with ara-C (200 mg/kg) 12 hr prior to each course of irradiation; 3.25-3.5 days after the last irradiation mice were inoculated with 3H-thymidine (20 uCi) and sacrificed 40 min later. The number of regenerating crypts in the transverse section of jejunum was assessed autoradiographically. The effect of ara-C before a range of doses (3-14 gray) was evaluated by a second assay dose of 13 gray 12 hr after the first dose. It was found that administration of ara-C resulted in significant enhancement of survival equivalent to a dose reduction of 4-5 gray. The optimum time interval for ara-C pretreatment was different for bone marrow colony forming unit-stem cells (CFU-S) and intestinal clonogenic cells. (5 Refs)

63. EFFECT OF POLY-U:POLY-C INTERFERON ON BONE MARROW CELL METABOLISM IN ALBINO MICE SUBJECTED TO WHOLE-BODY X-RAYS

Ternovy MK
Inst. Orthopedics, Kiev, USSR
Dopov Akad Nauk Ukr RSR kSer Bl; (9):839-841 1977

The radioprotective effect of interferon (IF) was studied in random bred albino mice. Animals received an intraosseous injection of polyuridylic acid:polycytidylic acid (polyU:polyC)-IF (0.2 mg/kg) and 2 hr later underwent whole-body irradiation with X-rays (550 R). To determine the rate of DNA, RNA, and protein synthesis in bone marrow cells, mice were injected with H3-thymidine, H3-uridine, and H3-phenylalanine (5 mCi/kg, ip). The inhibition of DNA synthesis caused by exposure to X-rays was significantly lower in animals treated with the polyU:polyC-IF complex than in those not given the radioprotector. (12 Refs)

64. INITIAL STUDIES OF HYPOXIC RADIOPROTECTION BY DEOXYGENATED DEXTRAN-HEMOGLOBIN

Hill RP, Porter LS, Ives SA, Wong JT
Department of Medical Biophysics, University of Toronto, Ontario, Canada.
Int J Radiat Oncol Biol Phys; 10(3):369-73 1984

Initial studies were performed to examine the potential of perfused dextran-hemoglobin to protect pig skin or mouse bone marrow cells against radiation damage. Some protection was indicated in both systems. In the pig skin a protection factor of 1.5 was observed for moist desquamation, and 2.0 for necrosis. These results suggest the possibility of using blood substitutes to induce tissue hypoxia f or therapeutic purposes.

65. DETERMINATION OF THE RADIOPROTECTIVE EFFECTS OF TOPICAL APPLICATIONS OF MEA, WR-2721, AND N-ACETYLCYSTEINE ON MURINE SKIN

Verbey LJ, Sedlacek R
Div. Radiation Biophysics, Dept. Radiation Medicine, Massachusetts General Hosp., Harvard Medical Sch., Boston, MA. 02114
Radiat Res; 93(1):175-183 1983

Single doses of 137Cs irradiation were used to investigate the protective effects of topical applications of N-acetylcysteine (NAC), beta-mercaptoethylamine (MEA), in both buffered and nonbuffered forms, and WR-2721 on murine skin. The effects of the level of oxygenation of the skin on the radioprotective properties of buffered MEA were examined. No significant skin protection was afforded by WR-2721 with either a 15-or 60-min soak period or by NAC. This might be due to an inability of these drugs to permeate the keratin layer of epidermis. An alternate explanation of the apparent absence of protection of skin for topically applied WR-2721 could be inefficient hydrolysis of the compound into free thiol. MEA showed an ability in all forms used in the experiments to protect skin against acute radiation damage but not against late contraction of the skin. The use of topical MEA on unanesthetized animals breathing carbogen (95% O2, 5% CO2) appeared to give an enhanced level of radioprotection over that shown for anesthetized, air-breathing animals. MEA can offer a high level of protection of well-oxygenated normal skin against acute radiation damage. MEA, particularly in the buffered form appears to be nontoxic and should be pursued for possible future use on human skin being unavoidably irradiated to high doses. (22 Refs)

66. SKIN RADIOPROTECTION BY 5-THIO D-GLUCOSE

Schuman VL, Clement JJ, Levitt SH, Song CW
Dept. Therapeutic Radiology, Univ. Minnesota Medical Sch., Box 494 Mayo Hosp., Minneapolis, MN, 55455
Radiat Res; 93(2):326-331 1983

The radioprotective effect of 5-thio-D-glucose (5TG) was investigated and compared to that of S-2-(3-aminopropylamino)ethylphosphorothioic acid (WR-2721), an aminothiol radioprotector, using the mouse foot system. Skin reactions and foo. deformity were scored according to a previously described arbitrary scale. Following 4,000 rad of x-irradiation, significant skin reactions began to develop after 10 days in both 5TG and saline treated animals. Skin reactions in the saline-treated animals peaked at 18-21 days postirradiation with a mean score of 3.0, then decreased to 2.0 by day 27, at which level they remained through day 40. Skin reactions in 5TG mice, however, began to subside after peaking on day 13 with a mean score of 1.3. By day 40 only minimal foot damage remained. 5TG also was radioprotective against late deformity due to x-irradiation. By day 90, when 10/11 saline-treated animals had severely deformed feet, only 2/11 5TG animals had deformed feet. After 137cesium gamma irradi ation in the range of 3,500-5,500 rad, the dose modification factors of 5TG were 1.3 and 1.2 for max and av skin reactions, respectively, compared to values of 1.5 for both parameters for WR-2721. (14 Refs)

67. QUANTITATIVE EVALUATION OF THE EFFICACY OF RADIOMODIFIERS DURING LOCAL IRRADIATION OF THE SKIN

Vygodskaia AL, Vinskaia NP, Krimker VM
All-Union Cancer Res. Center, Moscow, USSR
Med Radiol (Mosk); 27(3):52-55 1982

The radiomodifying activity of aminopropylaminoethylthiophosphate (WR-2721) and metronidazole (MZ) was studied in SHK mice subjected to local irradiation of the hindlimbs (608 rads/min). Analysis of the degree of acute radiodermatitis showed that WR-2721 administration reduced the radiation injuries of the skin. MZ had a marked radiosensitizing effect. (27 Refs)

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68. PROTECTION OF NORMAL TISSUE AGAINST LATE RADIATION INJURY BY WR-2721

Utley JF, Quinn CA, White FC, Seaver NA, Bloor CM
Dept. Radiology, Div. Radiation Oncology, Univ. California San Diego, San Diego, CA, 92103
Radiat Res; 85(2):408-415 1981

Acute and chronic radioprotective effects of S-2(3-amino propylamino)ethylphosphorothioate (WR-2721) were studied in skin, skeletal muscle, and blood vessels of irradiated rats. Treated rats received 200 mg WR-2721/kg, ip, 15 min before irradiation of the left hind limb with single doses of 2,000, 4,000, 6,000, or 8,000 rads of 60Co gamma rays. Untreated rats were irradiated at the same doses, but did not receive WR-2721. Control rats were not irradiated or treated with WR-2721. Acute and chronic changes were studied in the skin, skeletal muscle, and blood vessels of the hind limbs over a 6-mo period. Comparison was made of differences in the left and right hind limbs of each animal, and of differences between treated, untreated, and control animals. Acute skin changes were most severe at 2-3 wk and healed by 4-6 wk; complete healing occurred in both treated and untreated rats that received 2,000 rads. Acute changes were generally parallel for treated and untreated rats at each dose, but the changes were consistently lower in the treated animals. This lower degree of radiation injury in the drug-treated animals was most pronounced in the 6,000-rad group. These results were utilized in calculating an acute dose-modifying factor (DMF) for radiation injury to skin of 1.5. Muscle fiber atrophy occurred as early as 1 wk after irradiation in the untreated rats. At most of the time and dose points examined, the difference in degree of muscle fiber atrophy between treated and untreated rats was significant, indicating drug protection. These findings were utilized in calculating a DMF for late radiation injury in muscle of 1.5-2.0. Also vascular radiation injury in the treated rats was significantly less than that in the untreated rats, indicating drug protection. (22 Refs)

69. PROTECTION OF SPERMATOGONIAL SURVIVAL AND TESTICULAR FUNCTION BY WR-2721 AGAINST HIGH AND LOW DOSES OF RADIATION

Meistrich ML, Finch MV, Hunter N, Milas L
Department of Experimental Radiotherapy, University of Texas M.D. Anderson Hospital and Tumor Institute at Houston.
Int J Radiat Oncol Biol Phys; 10(11):2079-107 1984

The radioprotection of normal cells with WR-2721 at doses of radiation extending down to less than 1 Gy was investigated using testicular cells. Survival of stem spermatogonia after single doses of radiation was measured by counts of repopulating tubules and by sperm head counts, with consistent results obtained for both endpoints. Protection factors (PF) obtained by injection of 400 mg/kg WR-2721 at 15 min prior to irradiation decreased from about 1.4 at radiation doses above 10 Gy to 1.0 at 2 Gy. Similarly, the radioprotection by 300 mg/kg WR-2721 was reduced from a PF of about 1.35 when the drug was given prior to a single high dose of radiation to 1.0-1.1 when the drug was given prior to each of 5 daily fractions of 2 Gy. Thus, less protection of testicular stem cells by WR-2721 was observed at lower doses of radiation. This lowered protection may be explained, at least in part, by a direct cytotoxic effect of WR-2721 on testicular stem cells. Protection of differentiated spermatogonia was observed with 400 mg/kg WR-2721; the PF was 1.4 at 1 Gy and decreased at lower doses. The protection of testicular function by WR-2721, as assayed by the return of fertility and the maximum recovered level of sperm production, was compared to the protection of stem cell survival. At about 8 Gy the PF with 400 mg/kg WR-2721 for both functional endpoints was about 1.5, which was not significantly different from the value of 1.3 obtained using the stem cell assays.

70. EFFECTS OF S-2(3-AMINOPROPYLAMINO) ETHYLPHOSPHOROTHIOIC ACID (WR-2721) ON THE SENSITIVITY OF MOUSE SPERMATOGONIA A TO RADIATION

Jaimala, Bhartiya HC, Pareek BP
Department of Zoology, University of Rajasthan, Jaipur, India.
Acta Radiol Oncol; 23(1):65-8 1984

The sensitivity of spermatogonia to radiation was investigated in adult male Swiss albino mice after whole body exposure to three different doses (3, 6 and 8 Gy) of gamma radiation from a 60Co source with or without the drug S-2-(3-aminopropylamino) ethylphosphorothioic acid (WR-2721), at a dose of 400 mg/kg body weight. Spermatogonia A were counted in the seminiferous tubules of the testis, taken at post-irradiation intervals of 1, 2, 4, 7, 10, 14 and 28 days in both the drug treated and the control mice. The spermatogonia A count decreased after all three exposures. Severe depletion was observed with the higher dose (8 Gy) at early intervals. Recovery started at day 14, but normal counts could not be attained even up to the last interval. A similar pattern was observed with 6 and 3 Gy, but the number of counts was comparatively larger than with the 8 Gy group and the recovery was also faster in these groups. In all the drug treated groups, the spermatogonia A counts were always higher than their respective controls, showing an appreciable protective potential of WR-2721 against radiation.

71. CYTOTOXIC EFFECTS OF WR-2721 ON MOUSE TESTICULAR CELLS

Meistrich ML, Finch MV, Hunter N, Milas L
Department of Experimental Radiotherapy, University of Texas M.D. Anderson Hospital and Tumor Institute at Houston.
Int J Radiat Oncol Biol Phys; 10(9):1551-4 1984

WR-2721 (S-2-(3-aminopropylamino)ethylphosphorothioic acid) has been demonstrated to be cytotoxic to stem spermatogonia in the mouse. Five and 10 injections of 300 mg/kg killed sufficient numbers of stem cells to reduce sperm production 56 days after treatment by 16 and 43%, respectively. Single injections of 300 or 400 mg/kg of WR-2721 given 15 min after irradiation produced negligible toxicity to stem cells as measured by counts of repopulated tubules; 600 mg/kg reduced stem cell survival by 47%. Four daily injections of 300 mg/kg given 4, 3, 2, and 1 days prior to irradiation (with or without a fifth injection 15 min after irradiation) reduced stem cell survival by about 60%. The cytotoxic effects of WR-2721 on testicular stem cells at least partially explains the reduced protection factors observed in the testis with low doses of radiation and during fractionated treatments involving multiple injections of drug.

72. PROTECTION OF MICROCIRCULATION IN RAT BRAIN AGAINST LATE RADIATION INJURY BY GAMMAPHOS

Plotnikova ED, Levitman MK, Shaposhnikova VV, Kosheyoy JuV, Eidus LK
Institute of Biological Physics of Academy of Sciences, U.S.S.R., Puschino, Moscow Region.
Int J Radiat Oncol Biol Phys; 10(3):365-8 1984

The ability of a radioprotector-gammaphos to modify the development of late vascular changes in the rat brain after local irradiation with 40 and 60 Gy was investigated by means of an angiographic method. The relative number of animals with gross vascular abnormalities, the size of foci with vascular lesions, and the changes in size and number of vessels were less in the drug-treated groups. Thus, it may be possible to increase the tolerance of host tissues to curative radiation therapy by chemical radioprotectors such as gammaphos.

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73. WR-2721 PROTECTION OF PNEUMONITIS AND FIBROSIS IN MOUSE LUNG AFTER SINGLE DOSES OF X RAYS

Travis EL, Parkins CS, Holmes SJ, Down JD, Fowler JF
Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex, England.

Int J Radiat Oncol Biol Phys; 10(2):243-51 1984

The radioprotective effect of WR-2721 has been studied in mouse lung after single doses of radiation. Using the breathing rate assay and lethality, radioprotection was assessed at monthly intervals between 3 and 18 months after irradiation during both pneumonitis and chronic fibrosis. The degree of radioprotection was greater for fibrosis than for pneumonitis using both assays. In replicate experi ments, dose modifying factors (DMF's) ranging from 1.2 to 1.4 were obtained for pneumonitis and 1.5 and 1.6 for fibrosis. The differences in DMF's for the two phases of lung damage were significant. A difference in the time course of expression of damage was seen in both the breathing rate and lethality assays between mice irradiated with and without WR-2721: the damage ended sooner in the drug-treated mice. This difference is best explained by protection of all damage after 5 months by WR-2721. No evidence of drug toxicity was found. We conclude that WR-2721 protects against chronic lung fibrosis caused by radiation at least as well as against the earlier appearing pneumonitis after single doses of radiation. Thus, if WR-2721 is dose modifying and if late tissue complications are dose limiting in clinical radiotherapy, then a therapeutic benefit would be obtained by the use of this drug in clinical radiotherapy, provided that the radioprotection of tumors did not exceed a factor of 1.5-1.6.

74. THE RADIOPROTECTIVE EFFECT OF N-ACETYLCYSTEINE INHALATION ON THE TOLERANCE OF THORACIC RADIATION IN MICE (MEETING ABSTRACT)

Lesli NT, Amato DA, Hellman S
Joint Center for Radiation Therapy, Harvard Medical School, Boston, MA

Proc Annu Meet Am Assoc Cancer Res; 25:342 1984

The lungs are the major limiting normal tissue in total body irradiation (TBI) for bone marrow transplantation (BMT). Interstitial pneumonitis (IP) remains an important clinical problem and although multifactorial in origin, radiation appears to contribute to its development. The addition of a selective radiation protector of the lungs could ameliorate this problem. N-acetylcysteine (NAC), a sulfhydryl compound with known radioprotective properties, appears ideal. This experiment was designed to study the effects of NAC inhalation on the tolerance of the lungs and the upper aerodigestive tract to radiation. Mice were given single fraction doses of irradiation from 1000-1900 rads at high dose rate. Esophageal deaths were calculated from deaths occurring within 30 days. The LD50/30 for the control group was 1488 rad (1460-1508) compared with 1512 (1490-1533) in the NAC treated group. NAC treated mice had a slightly lower rate of esophageal death compared with the control group ($p=0.13$, exact contingency table test). Deaths occurring between 30-180 days were ascribed to pulmonary toxicity. The pulmonary LD50/180-30 for the NAC mice was 1322 rads (1295-1355) compared to 1299 rads (1263-1336) for the control group. To assess the overall effect of treatment a Cox model was fitted with treatment, dose and experimental group as covariants. The NAC mice had significantly better survival than the controls for the 1400 rad group (($p=.007$), log rank test). Using the entire group this analyses indicates that thIe NAC mice had superior survival compared to control mice ($p=0.04$). As expec ted, dose was highly significant ($p=0.0001$). This study indicates that NAC may be useful as a selective pulmonary radiation protector. Ultimately, this may be useful in patients undergoing TBI for BMT in the treatment of malignant diseases.

75. PROTECTION OF NORMAL TISSUES WITH 2-AMINOETHYLISOTHIOURONIUM DURING LOCAL PELVIC RADIATION IN MONKEYS

Ambrus CM, Ambrus JL, Friedman M, Pickren JW, Mirand EA, Kisbel SP
Roswell Park Memorial Institute, Buffalo, New York.

Cancer Res; 43(6):2857-61 1983

Intestinal and bladder injury are the main limiting factors to radiation therapy in patients with pelvic neoplasms. 2-Aminoethylisothiouronium (AET) is a radiation-protective agent when given systemically but absorbs poorly from the intestines. Accordingly, it was explored for the local protection of the bowel and bladder during radiation to the pelvis. Radiation localized to the pelvis in various high fractionated doses and various schedules was applied to pairs of stumptailed monkeys (Macaca arctoides): one was always a control; and the other was treated with AET. AET was applied to the bladder through a carheter and to the rectum with a cotton tampon during the time of radiation. After radiation, AET was removed by repeated washings. Control animals developed hemorrhage, diarrhea, and emaciation and died at various times after completion of the radiation course; biopsy of rectal mucosa showed severe radiation damage. AET-treated animals had only occult blood in the stools and suffered slight weight loss; rectal biopsies showed normal tissues 2 weeks after radiation.

76. 16, 16-DIMETHYL PROSTAGLANDIN E2 INCREASES SURVIVAL OF MURINE INTESTINAL STEM CELLS WHEN GIVEN BEFORE PHOTON RADIATION

Hanson WR, Thomas C
Section of Radiobiology, Rush University-Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois.

Radiat Res; 96(2):393-8 1983

A variety of prostaglandins (PG) protect the gastric and intestinal mucosa when given before damaging agents such as absolute ethanol, acidified taurocholate, boiling water, or nonsteroidal anti-inflammatory agents (NSAI). A synthetic prostaglandin, 16, 16-dimethyl PGE2, shown to be cytoprotective at physiologic levels to the above agents was given to mice 1 hr before or 15 min after 137Cs gamma (gamma) whole-body irradiation. The survival of intestinal stem cells measured by their ability to form in situ colonies of regenerating epithelium was increased when 16, 16-dimethyl PGE2 was given before but not after 137Cs gamma irradiation. The maximum degree of 16, 16-dimethyl PGE2-induced radioprotection was seen when the drug was given 1 hr before irradiation. No radioprotection was seen when the interval between drug and irradiation was 3 hr or longer. When the time between 16, 16-dimethyl PGE2 and irradiation was kept at 1 hr, the degree of radioprotection was dependent on the PG drug d ose. There was a steep rise in the number of surviving cells at low doses of PG. These results imply that tumors which secrete PGE2 may in part be protected from the lethal effects of ionizing photon radiation.

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77. IMMEDIATE AND LONG-TERM EFFECTS OF IRRADIATION AND PERITOL ADMINISTRATION ON THE STATE OF THE SMALL INTESTINE

Brodskii RA, Dedenkov AN, Iavor T, Khachirov DG, Bero T, Bandurko LN, Iakovleva ND, Kudriavtsev VD, Sushkevich LN, Pogudina NA, Gorobets VF, Ispenkova LI

Res. Inst. Medical Radiology, Obninsk, USSR

Med Radiol (Mosk); 27(7):65-70 1982

The functional state of the small intestine was studied in male Wistar rats subjected to partial irradiation of the abdominal region (700 rads, 5x, qod) and ip administration of the anabolic steroid Peritol. Analysis of the immediate and long-term radiation effects showed that the Peritol administration enhanced the recovery of the number of crypts in the irradiated small intestine and increased the functional activity of the endothelium of the intestinal mucosa. (10 Refs)

78. THE RADIOPROTECTIVE EFFECT OF 5-THIO-D-GLUCOSE ON NORMAL TISSUES IN VIVO

Schuman VL, Levitt SH, Song CW

(c/o Song) Dept. Therapeutic Radiology, Box 494, Univ. Minnesota, Mayo Hosp., Minneapolis, MN, 55455

Int J Radiat Oncol Biol Phys; 8(3/4):589-591 1982

Female A/J mice were injected ip with 1.5 g/kg of 5-thio-D-glucose (5-TG) 2 hr prior to x-irradiation (whole-body or to the right foot). 5-TG-injected mice were protected from gastrointestinal or bone marrow death following whole-body irradiation by a dose modification factor (DMF) of 1.1-1.3. Mice were protected from skin damage to the foot up to 40 days after irradiation by a DMF of 1.3 and from late foot deformity during 60-90 days after irradiation by a DMF of 1.2. Max protection occurred for up to 4 hr after an ip injection of 5-TG. (11 Refs)

79. MODIFICATION OF RADIATION SENSITIVITY IN LIVER BY 2-MERCAPTOPROPIONYLGLYCINE (MPG): A QUANTITATIVE EVALUATION

Gupta ML, Jagetia GC, Kumar S, Kumar A, Devi PU

Radiation Biology Lab., Dept. Zoology, Univ. Rajasthan, Jaipur, India

Radiobiol Radiother (Berl); 23(4):429-432 1982

Protection effects of 2-mercaptopropionylglycine (MPG) in liver against external gamma radiation was investigated in adult Swiss albino mice exposed to 750 R of gamma irradiation. Results suggested that MPG protected liver cells against gamma irradiation as indicated by a lower percentage of abnormal cells in experimental animals and an accelerated recovery process of the animals. (13 Refs)

80. CHEMICAL PROTECTION OF MOUSE INTESTINE AGAINST GAMMA RAYS WITH 2-MERCAPTOPROPIONYLGLYCINE (MPG)

Uma Devi P, Mathur VB

Radiation Biology Lab., Dept. Zoology, Univ. Rajasthan, Jaipur 302 004, India

Indian J Exp Biol; 19(4):396-398 1981

The radioprotective action of 2-mercaptopropionylglycine (MPG) on the ileum of male albino mice after exposure to a sublethal dose of gamma radiation was studied. The results indicated that MPG protects the intestinal epithelium and accelerates the recovery process. This was indicated by the fact that the values of total cell and mitotic figures in the protected animals remained significantly higher than in the unprotected controls whereas the number of pyknotic nuclei and necrotic cells showed significantly lower values in the former. (22 Refs)

81. THE RADIOPROTECTIVE EFFECT OF MISONIDAZOLE (RO-07-0582) ON NORMAL CANINE RECTUM

Stryker JA, Albert A, Abt AB

Div. Radiation Oncology, M. S. Hershey Medical Center, Hershey, PA, 17033

Strahlentherapie; 156(10):719-724 1980

A single 1,500 rad (= 15 Gy) dose of 10 MeV x-rays was administered to the pelvis of 20 mongrel dogs. Ten received misonidazole (Ro-07-0582), 100 mg/kg po, 4 hr pre-irradiation. Serum misonidazole levels immediately pre-irradiation were 43 +-10 ug/ml (mean +- SD). The dogs were euthanized within 3 mo post-irradiation. Each rectal specimen was studied for anatomic and histologic pathology and was assigned a Pathologic Alteration Score (PAS) of 1, 2, or 3 in order of increasing severity. The PAS of the rectal specimens from the drug group was 1.6 +-0.7, and that of the controls 2.3 +-0.8. The PAS of the drug group was significantly lower than the control group ($p = 0.008$). The data suggest that misonidazole is a radioprotector for normal tissue. (Author abstract) (14 Refs)

82. TRIAL OF A NEW COMPOUND AS A CHEMICAL RADIOPROTECTOR AND ITS EFFECT ON MELATONIN

Hasan SS, Singh PM, Pandey SN, Prasad GC

Dept. Zoology, Garhwal Univ. Campus, Pauri (Garwhal) 246001, India

J Nucl Med Allied Sci; 24(3/4):135-137 1980

The mode of action and efficacy of 1-acetyl hydrazinyl thiophenyl formamidine dihydrochloride (AHTFD) as a radioprotector were investigated in rats. Administration of AHTFD (30 mg/kg) 30 min prior to total body irradiation (600 R) decreased the overall 30-day mortality rate from 60% to 0%. Treatment with AHTFD and radiation caused a significant decrease in melatonin content of the pineal gland on day 7, followed by an increase on day 14. In addition, this treatment caused a significant increase in serum protein bound iodine on day 14. (9 Refs)

83. BIS(3,5-DIISOPROPYLSALICYLATO)COPPER(II), A POTENT RADIOPROTECTANT WITH SUPEROXIDE DISMUTASE MIMETIC ACTIVITY

Sorenson JR

University of Arkansas College of Pharmacy, Little Rock.

J Med Chem; 27(12):1747-9 1984

Superoxide disproportionation may partially account for the noteworthy radioprotectant activity of bis(3,5-diisopropylsalicylato)copper(II) [CuII(3,5-dips)2]. Groups of mice treated with CuII(3,5-dips)2 3 or 24 h before exposure to a lethal dose of gamma-radiation had survival rates of 33% and 58%, respectively. These results suggest that copper complexes might be developed for protection of normal tissues in association with cancer radiotherapy and protection against occupational exposures to hazardous radiation.

84. STUDIES ON THE RADIOPROTECTIVE EFFECTS OF SUPEROXIDE DISMUTASE IN MICE

Abe M, Nishidai T, Yukawa Y, Takahashi M, Ono K, Hiraoka M, Ri N

Dept. Radiology, Faculty Medicine, Kyoto Univ., 606 Kyoto, Japan

Int J Radiat Oncol Biol Phys; 7(2):205-209 1981

The radioprotective effects of bovine liver Cu-Zn superoxide dismutase (SOD: given ip) were studied in Slc;ddy mice. In mice given SOD (1 mg/mouse) 1 hr before and 1 hr after total-body irradiation (6-10 Gy; 1 Gy equals 100 rads), the 30-day LD50 increased from 7.54 Gy (saline-treated controls) to 7.84 Gy. The cutaneous toxicity of one radiation dose (20 Gy) was reduced most when SOD was given 1 hr before and

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1 hr after irradiation (1 mg/mouse), followed by 0.5 mg/day for 27 days. The cutaneous toxicity of multiple radiation doses (5.73 Gy/day x 15 over 18 days) was reduced by SOD (0.5 mg/mouse, 1 hr before and 1 hr after fraction) at cumulative radiation doses less than approx 74 Gy (573 rads x 13 fractions), but not at or above 74 Gy. Foot deformities induced by one radiation dose to the hindlimb were reduced by SOD (1 mg/mouse, 1 hr before and 1 hr after radiation) at doses of 40-70 Gy, but not at the lowest radiation doses. (11 Refs)

85. RADIOPROTECTIVE EFFECTS OF SUPEROXIDE DISMUTASE (SOD) ON MURINE TISSUES

Nishidai T, Ono K, Ri N, Hiraoka M, Takahashi M, Abe M
Dept. Radiology, Faculty Medicine, Kyoto Univ., Kyoto, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 40(10):983-990 1980

Radioprotective effects of Cu,Zn-superoxide dismutase (Cu,Zn-SOD) using Slc; ddy mice were studied. The dose required to kill 50% of the SOD-treated mice within 30 days (LD50/30) was 7.85 Gy as compared to 7.54 Gy for the control group of mice. The difference between these two groups was statistically significant. Protective effects of SOD on radiation induced skin reactions of mice were examined as a function of the drug concentration and the administration modes. The anti-inflammatory effects of SOD were most prominent when 1 mg/mouse of SOD was given ip 1 hr before and 1 hr after irradiation, and thereafter, 0.5 mg/mouse daily. Protective effects of SOD as a function of radiation dose were examined using deforming scores for the mouse leg as a measure of response. Protective effects of the drug were observed in the range of 50-70 Gy, while no effect was obtained in the dose level less than 50 Gy. (Author abstract) (22 Refs)

86. MODIFICATION OF RADIATION INJURY BY DIBASIC SULFUR-CONTAINING ACIDS OF THE PHENOL SERIES

Kozhokaru AF, Alekseva LV, Ahmv IG
Inst. Biological Physics, Pushchino, USSR
Radiobiologiia; 22(4):545-548 1982

Potential radioprotective effect of dibasic sulfur-containing acids of the phenol series was studied in male random-bred mice and in male Wistar rats. The animals were subjected to a single whole body irradiation (750-800 rads for the mice; 900 rads for the rats). The sulfur-containing compounds (60-80 mg/kg) were administered 60 min prior to irradiation. Survival rates in the irradiated mice and rats that were administered the sulfur-containing compounds were 70-100%, compared with 0-10% in irradiated animals that were not administered the compounds. The radioprotective activity of the compounds depended upon the nature of the substituent in the benzene ring. (9 Refs)

87. RADIOPROTECTIVE EFFICACY OF CYSTAMINE ADMINISTERED INTRAMUSCULARLY TO MICE

Kuna P
J. Purkyne Medical Res. Inst., Hradec Kralove, Czechoslovakia
Radiobiologia; 22(4):517-519 1982

Acute toxicity and radioprotective activity of cystamine (CA) were studied in female random-bred albino mice that were subjected to whole-body gamma irradiation (66.2-71.5 rads/min); the CA was injected im or ip (150 or 175 mg/kg) 10 min prior to the irradiation. The acute toxicity of the CA after the im administration was similar to that after the ip administration. The radioprotective activity of the CA was determined on the basis of the LD50 of the irradiation 30 days after it was administered. The LD50 after im administration of the CA at 150 mg/kg was 1,122 rads, compared with 1,110 rads after ip administration at the same dose and 717 rads for untreated controls. The radioprotective activity of the CA after im administration at 175 mg/kg was greater than that after ip administration at this dose. Increase in the interval between administration and irradiation to 2 hr reduced the radioprotective activity of the CA. (3 Refs)

88. ONSET OF RADIOPROTECTIVE EFFECT OF GAMMAPHOS (WR-2721) IN MICE

Kuna P
Vojensky lekarsky vyzkumny a doskolovaci ustav J. E. Purkyne, 502 60 Hradec Kralove, Czechoslovakia
Cas Lek Cesk; 121(29):912-914 1982

Gammaphos, administered to mice ip, im or sc 5 or 10 min before whole-body gamma irradiation (dose rates 33.2 or 34 rads/min), was found to exert potent protective effects against lethal irradiation. When gammaphos was administered 10 min before irradiation at doses of 1,300-1,600 rads, the dose reduction factors were found to be 2.03 (1.86-2.23) for sc, 2.15 (1.9-2.42) for ip, and 2.33 (2.07-2.91) for im administrations. (6 Refs)

89. RADIOPROTECTIVE PROPERTY OF FLAVONOIDS IN MICE

Agarwal OP, Nagaratnam A
Div. Pharmacology, Indian Inst. Experimental Medicine, 4, Raja S. C. Mullick Road, Calcutta 700 032, India
Toxicon; 19(2):201-204 1981

The radioprotective properties of nepitrin (NEP), scutellarein (SCU), rutin (RUT) and naringin (NAR), after po administration were investigated. One hundred and thirty inbred mice of either sex were exposed singly to graded doses of gamma radiation in a 60Co irradiation chamber. Animals of Group I were exposed to radiation alone with no drug, or no irradiation (controls). Animals of Group II received no medication or irradiation (controls); vehicle (propylene glycol) and irradiation (irradiated control); or NEP, SCU, or NAR (100 mg/kg/day for 2 days and 30 min before irradiation on the third day); and RUT (70 mg/kg/day po for 14 days); and one subgroup received aminoethylisothiuronium bromide (AET: 400 mg/kg, po 30 min before irradiation). All animals except those not irradiated received a lethal dose of radiation and mortality at 30 days was noted. NEP, SCU, and NAR showed radioprotective action: mean survival of control irradiated mice was 11 +-3 days; with NEP it was 17 +-5 days, with SCU 14 +-5 days, with RUT 21 +-7 days, and with NAR 14 +-4 days. Those pretreated with AEF survived for the entire observation period (30 +-6 days). Both NEP and RUT inhibited the increase in cutaneous capillary permeability induced by histamine in mice. (11 Refs)

90. EXPERIMENTAL DATA ON THE USE OF CERTAIN ISOTHIURONIUM DERIVATIVES AS RADIOPROTECTORS

Goloshchapova ZhA, Tuzhilkova TN, Mizrakh LI
No affiliation given
Radiobiologiia; 21(4):521-525 1981

The radioprotective activity of diethylphosphate and metaphosphate of S-alkylisothiuronium (compounds I and II) was studied in C57Bl/6 mice and albino rats. Administration of I and II prior to whole-body gamma-irradiation at 154.8-258.0 mCi/kg provided a 40-70% survival of irradiated animals. The factor of dose reduction for compounds I and II was 1.14 and 1.19, respectively, after ip administration, and 1.12 and 1.17, respectively, after im administration. (8 Refs)

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91. ACUTE TOXICITY AND RADIOPROTECTIVE EFFECTIVENESS OF WR-2721 (GAMMAPHOS) IN RATS

Kuna P, Krajcovic C

Vojensky lekarsky vyzkumny a doskolovaci ustav J.E. Purkyne, 502 60 Hradec Kralove, Czechoslovakia

Cas Lek Cesk; 120(25):776-778 1981

The im and ip LD50 values for Gammaphos [WR-2721; thiophosphoric acid S-2-(3-aminopropylamino)ethyl ester] were found to be 441 and 463 mg/kg, respectively, in rats. Administered in doses of 150-250 mg/kg in 15 min before whole-body telecobalt irradiation (38.6-38.1 rads/min), Gammaphos reduced significantly the mortality of the rats during the first 30 days after irradiation. (8 Refs)

92. STUDIES OF THE EFFICIENT RANGE OF RADIATION PROTECTION OF SODIUM CITRATE USING MATHEMATICAL PLANNING

Ivanov AA, Mozaiskij AM

Dubninskaja 12, korp. 1, kv. 341, 127540 Moskau, USSR

Radiobiol Radiother (Berl); 22(6):787-792 1981

The protective effect of sodium citrate (NaC) in mice undergoing gamma-irradiation was studied using the Greek-Latin square method. The effects of various radiation dose, amount, type, and timing of NaC administration were determined. Maximum radioprotective effect was obtained in 18-20 g mice receiving lethal irradiation when 0.4 ml 5% NaC/mouse was injected parenterally. Survival was increased to 32-40% compared with controls. Decreasing radiation dose or increasing the interval between inject ion and irradiation reduced the protective effect of NaC. (8 Refs)

93. RADIOPROTECTIVE ACTIVITY OF NEW BETA-AMINONITRILES

Babaev RA, Akhmedov RM, Mekhtiev SI, Kuliev TA, Dzhaharov MI

A. I. Karaev Inst. Physiology, Acad. Sciences Azerbaijan SSR, Baku, USSR

Radiobiologiia; 20(5):750-752 1980

Experiments conducted with 60 irradiated Wistar rats showed that beta-aminobutyronitrile and beta-diethylaminobutyronitrile produced radioprotective effects: they increased the survival rate and the median life span. (10 Refs)

94. GENERAL CHARACTERISTICS AND COMPARATIVE EVALUATION OF RADIOPROTECTIVE PROPERTIES OF ADRENOMIMETICS OF THE ARYLALKYLAMINE SERIES IN EXPERIMENTS ON MICE

Kulinskii VI, Iasbunskii VG

Dept. Biochemistry, Medical Inst., Krasnoiarsk, USSR

Biull Eksp Biol Med; 87(3):232-233 1979

The radioprotective effect and toxicity of a series of arylalkylamines (AAA) were compared with the corresponding properties of aminothiols (AT). CBA mice, used for the tests, were inoculated with AAA sc 15 min prior to irradiation or with AT ip 7 min prior to irradiation. The dose of radiation was 800 rads. Three AAA (phenylephrine, ethylephrine, and nor-phenylephrine) and two AT (cystamine and aminoethylisothiuronium) were tested. It was found that AAA provided protection at relatively low doses (25-50 uM/kg, compared with 600-670 uM/kg for AT). The survival rate of animals treated with AAA was 80-88%, compared with 75% in animals treated with AT. (14 Refs)

95. CHEMICAL PROTECTION AGAINST THE LONG-TERM EFFECT OF A SINGLE WHOLE-BODY EXPOSURE OF MICE TO IONIZING RADIATION. II. CAUSES OF DEATH

Maisin JR, Declerc A, Gerber GB, Masselin G, Lambiet-Collier M

Dept. Radiobiology, C.E.N/S.C.K., B-2400 Mol, Belgium

Radiat Res; 74(3):415-435 1978

Diseases causing death in control mice and irradiated mice in the presence and absence of radioprotective agents were recorded to establish which diseases were responsible for radiation-induced shortening of life. Male BALB/c/CNb or C57B1/Cnb strain mice (4 and 12 wk old, 25 to 30 g; LD50/30 values 576 and 650 R, respectively) were treated with 2-beta-aminoethylisothiouronium-BR-H Br (AET) alone, with 5-hydroxytryptamine (5-HT) alone, or with a mixture of radioprotectors, including glutothione, cysteine, AET, mercaptoethylamine (MEA) and 5-HT. The mice were given single x-ray exposures ranging from 100 to 2,000 R depending on the treatment. Other groups served as irradiated nonprotected and nonirradiated controls. Mice were examined daily and, upon death, specimens of all important organs and diseased tissues were removed for histological examination. Irradiation of BALB/c mice resulted in greater than normal incidence of thymic lymphoma, which increasesd to a max at 650 R, declined at higher exposures and developed 150 to 500 days postirradiation. Lung and other carcinomas occurred with a shorter latency period after higher exposures. There was a significant increases in all leukemias after exposure to 350 R or greater. Irradiated C57B1 mice displayed marked increases in thymic lymphoma and all carcinomas. Liver tumors were affected significantly by 350 R but not by 650 R. Glomerulosclerosis and non-cancerous lung lesions contributed largely to death in both sets of mice in the high dose range. The principal mechanism for the prolonged lifespan of he irradiated mice was protection against thymic lymphoma. Protection was also possible against liver tumors, all carcinomas, leukemias, glomerulosclerosis, and noncancerous lung lesions. (23 Refs)

96. EFFECT OF RADIOPROTECTORS AFTER ADMINISTRATION BY INHALATION

Zherebchenko PG, Besedina LN, Borisov VP, Znamensky VV, Shomorokhova TN, Terekhov AV, Titov BA

No affiliation given

Med Radiol (Mosk); 23(2):74-77 1978

To avoid the side-effects of po administration of radioprotectors, inhalation administration was tested in CBA x C57B1 mice. The animals inhaled the diethylphosphate salt of S-ethylisothiouronium, thiophosphateacetamide, and Mesaton for 5 min and then underwent whole-body irradiation (950 R). The inhalation of the tested radioprotectors produced marked radioprotective effect: 40 to 55% of the animals survived 30 days (all control mice died within 30 days of irradiation). (16 Refs)

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97. CHEMOPROTECTION AGAINST THREE MODES OF RADIATION DEATH IN THE MOUSE

Yuhas JM, Storer JB
Int J Radiat Biol; 15(3):233-237 1969

B.

Protection Against Different Types of Radiation

98. STUDIES ON LET DEPENDENCE OF THE RADIOPROTECTIVE EFFECT OF WR 2721 (MEETING ABSTRACT)

Afzal SM, Mahlmann LJ, Ainsworth EJ
Biology and Medicine Div., Lawrence Berkeley Lab., Univ. of California, Berkeley, CA 94720
Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 43, 1985.

Reported here are the radioprotective effects of WR 2721 on the colony forming units-spleen (CFU-S) exposed to the heavy-ion beams with dose-averaged LET values ranging from 26 to 260 keV/um. CB6F1 mice were given total body doses of 20Ne, 28Si, 40Ar and 56Fe ions in the plateau region of the Bragg curve 30 min after an ip dose of 400 mg/kg of WR 2721. Marrow collected 30 to 90 min after irradiation was transplanted into supralethally irradiated syngeneic recipients and the CFU-S survival curves were computed. The magnitude of protection afforded by WR 2721 is significant at 26, 51 and even 135 keV/um LET values where the data were collected with 20Ne, 28Si and 40Ar ions, respectively. The largest component of protection is the slope change, where at LET values of 26 and 51 keV/um the DMFs are 2.1 and 2.3, respectively, which are very close to the gamma value of 2.4 (gamma LET approx equal to 0.8 keV um). Protection, however, decreased with increase in LET from 51 to 135 keV/um. Follow ing irradiation with very high-LET (260 keV/um) 56Fe ions, WR 2721 did not change the slope of the survival curve, but did displace it slightly to a higher dose range.

99. INTERFERON PRODUCTION BY AND RADIOPROTECTIVE EFFECT OF POLY I : C AND TILORONE IN MICE EXPOSED TO HELIUM ALPHA IRRADIATION

Talas M, Fedorenko B, Batkai L, Stoger I
National Institute of Hygiene, Budapest, Hungary.
Acta Microbiol Hung; 32(3):225-31 1985

Serum interferon production induced by poly I : C and tilorone and their radioprotective effect in mice exposed to He-alpha particles was studied. The results were compared to those observed after exposure of mice to acute 60Co-gamma irradiation. Interferon production induced by poly I : C was depressed by He-alpha irradiation less than that induced by tilorone. Treatment of mice with poly I : C or tilorone before He-alpha irradiation had no effect on the mortality of animals in contrast to the radioprotective activity of these compounds against 60Co-gamma irradiation.

100. ASSESSMENT OF ANTIRADIATION DRUGS IN WHOLE-BODY LETHALITY OR CELL SURVIVAL IN THE INTESTINE AND MARROW (MEETING ABSTRACT)

Sigdestad CP, Connor AM
Dept. of Therapeutic Radiology, Henry Vogt Cancer Res. Inst., Louisville, KY 40292
Thirty-Second Annual Meeting of the Radiation Research Society. March 25-29, 1984, Orlando, Florida, p. 106, 1984.

The following drugs were assayed for their effectiveness in protecting normal tissues against either Co-60 gamma or fission neutron irradiation: WR-1065, WR-2529, WR-109342, WR-151327, and WR-168643. The endpoints measured were the LD-50(6) and the LD-50(30). Cell survival was determined in the hematopoietic system using the endogenous spleen colony assay and in the intestine using Withers' microcolony assay. With neutron radiation the drugs listed above showed these respective dose modification factors (DMF's) for LD-50(6): 1.42, 1.47, 1.47, 2.23, and 1.23. For the LD-50(30) the respective DMF's were: 1.04, 1.40, 1.21, 1.34, and 1.25. Following Co-60 irradiation the DMF's for LD-50(6) were 1.63, 1.72, 1.40, 1.79, and 1.39. For the LD-50(30) the respective DMF's were: 1.41, 1.69, 1.22, 1.61, and 1.41. The cell survival studies utilizing in vivo cellular systems correlated with the whole-body lethality studies.

101. RADIOPROTECTION OF COLONY FORMING UNITS-SPLEEN AGAINST HEAVY CHARGED PARTICLE DAMAGE BY WR 2721 (MEETING ABSTRACT)

Javed Afzal SM, Mahlmann LJ, Prioleau J, Ainsworth EJ
Lawrence Berkeley Lab., Univ. of California, Berkeley, CA 94720
Thirty-Second Annual Meeting of the Radiation Research Society, March 25-29, 1984, Orlando, Florida, p. 37, 1984.

WR 2721 is known to protect a wide range of normal tissues against low LET radiation damage. Recently, protection against fission neutron damage to the gastrointestinal tract by thiophosphates was als o demonstrated. The present study was undertaken to determine the LET dependence of the radioprotective effect of WR 2721 on CFU-S using heavy charged particles. Donor CB6F1 mice were given total body doses of 40Ar (330 MeV/u) or 28Si (670 MeV/u) ions in the plateau region of the Bragg curve 30 min after an ip dose of 400 mg/kg of WR 2721. Marrow collected 30 to 90 min after irradiation was transplanted into supralethally irradiated syngeneic recipients and the CFU-S survival curves were computed. Results from replicate experiments with 40Ar ions (LET approx 130 keV/um) show WR 2721 produced a significant increase in the D(0) and a DMF of 1.2. Preliminary results with 28Si ions (LET approx 50 keV/um) indicate a DMF greater than 1.2. Additional experiments are in progress and DMF estimates for 28Si and 20Ne ions will be presented.

102. PIOTRON PION IRRADIATION OF CEREBRAL CAPILLARIES IN NEONATAL RATS. RELATIVE BIOLOGICAL EFFECTIVENESS AND RADIOPROTECTION BY 0-(BETA-HYDROXYETHYL)-RUTOSIDES

Landolt R, Arn D, Cordt I, Schappi K, Fritz-Niggli H
Institut fur Strahlenbiologie, Universitat Zurich, Postfach 64, CH-8029 Zurich, Switzerland
Radiat Environ Biophys; 21(2):75-80 1982

Effects of rutosides on pion-induced normal tissue damage were investigated in the microvasculature of the neonatal rat brain and radiation-induced petechial hemorrhages since 0-(beta-hydroxyethyl)-rutosides (BHER) were shown to have a significant radioprotective effect both in x-ray- and electron-induced radiation damage (RD) of the brain microvascular system. Pions of a multiport applicator (Piotron) of higher dose rate [1 Gray unit (Gy)/min] were used. The pion-induced RD in animals treated with physiological saline soln resulted in a mean score value of 3.77 +-0.15 that was similar to that obtained by pion irradiation alone without saline administration. Preirradiation treatment of the rats with BHER reduced the radiation effect significantly to a value of 2.91 +-0.15. The dose modifying factor (DMF) of the rutosides was between 1.2 and 1.3. DMF was 1.3 if calculated by dividing the score values of saline-treated rats by those of BHER-treated rats irradiated with the same dose of 4 Gy (DMFdose). DMF was 1.25 if the dose of 4 Gy applied to the saline-treated rats was divided by the dose needed to obtain the same effect in BHER-treated rats (DMFeffect).

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Considering the litter values both the DMFdose and DMFeffect were 1.3. It was concluded that ions, in spite of their low energy transfer component, may induce RD which is subject to modifications by drugs. (9 Refs)

103. EFFECT OF ADETURON ON SURVIVAL AND HEMATOPOIETIC SYSTEM OF MICE EXPOSED TO DIFFERENT TYPES OF IONIZING RADIATION

Gvozdeva NI, Cherikov KS, Nikolov I, Shitneva MF, Sidorov IA, Preobrazhenskii IuIu, Fedorenko BS, Pantev T

No affiliation given

Radiobiologiia; 22(5):614-618 1982

Radioprotective effect of adeturon (ATP and S-2-aminoethylisothiuronium salt) was studied in (CBA x C57Bl)F1 mice subjected to irradiation with fast neutrons, gamma rays, or x-rays. Adeturon was administered 10-15 min before and 15 min after irradiation (250 or 500 mg/kg, ip). Adeturon increased the survival of the mice irradiated with fast neutrons. Adeturon was less effective in mice irradiated with gamma or x-rays. Adeturon increased the bone marrow cellularity and the number of colony-forming cells in the irradiated mice. (11 Refs)

104. CHEMICAL PROTECTION AGAINST GASTROINTESTINAL RADIATION INJURY IN MICE BY WR 2822, WR 2823, OR WR 109342 AFTER 4 MEV X RAY OR FISSION NEUTRON IRRADIATION

Connor AM, Sigdestad CP

Dept. Therapeutic Radiology, Henry Vogt Cancer Res. Inst., J. Graham Brown Cancer Center, Univ. Louisville, Louisville, KY, 40292

Int J Radiat Oncol Biol Phys; 8(3/4):547-551 1982

The protective effect of WR 2822, WR 2823, and WR 109342 on the intestinal epithelium of C57Bl/6J mice irradiated with either 4 megaelectron volt x-rays or fission neutrons was investigated and compared to that provided by WR 2721. WR 2822 and WR 2823 showed slight protective effects with respect to gastrointestinal death and intestinal crypt survival. WR 109342 was very toxic and provided no protective effects. WR 2822 protected against lethal effects of fission neutrons almost as well as WR 2721, and both WR 2822 and WR 2823 produced greater protection in crypt survival assays for fission neutron irradiation than WR 2721. (14 Refs)

105. EFFICACY OF PROTECTIVE EFFECT OF AMINOPROPYLAMINO-ETHYLTHIOPHOSPHATE IN NEUTRON BEAM, GAMMA OR X-IRRADIATION OF MICE

Sedlmeier H, Metzger E, Jentzsch U, Weitzenegger E

Laboratorium fur experimentelle Radiologie, Ingolstadter Landstr. 2, 8042 Neuherberg, W. Germany

Strahlentherapie; 157(10):685-691 1981

The efficacy of the radioprotective agent aminopropylaminoethylthiophosphate (WR 2721) was tested against different kinds of radiation on female NMRI-mice. The animals were divided into four groups and were exposed to neutrons as main component, to secondary gamma rays in a tissue-equivalent phantom, to pure gamma rays and to x-rays respectively. The following dose reduction factors have been obtained: 1.05 for neutron-irradiation, 1.33 for gamma irradiation in tissue-equivalent phantom, 1.69 for pure gamma rays and 2.08 for x-rays. The protective agent WR 2721 is apparently more efficient against low LET radiation. The mechanism of protection has been discussed in this respect. (Author abstract) (17 Refs)

106. CYSTEAMINE AS A PROTECTIVE AGENT WITH HIGH-LET RADIATIONS

Bird RP

Radiological Res. Lab., Columbia Univ., Radiological Res. Accelerator Facility, Brookhaven Natl. Lab., Upton, NY, 11973

Radiat Res; 82(2):290-296 1980

The ability of cysteamine to protect against high-LET radiation was studied, using synchronized Chinese hamster V79 cells. At 75 milliM, cysteamine protected the cells against x-rays and against 90 and 170 keV/um helium ions. The approximate dose-modifying factor for G1/S cells decreased from 4.8 to 1.6 with increased LET value, and that for late-S cells decreased from 3.2 to 1.5. The shape of the high-LET survival curves for both cell cycle times was preserved as expected for a dose-modifying agent. (11 Refs)

107. THE EFFECT OF S-2-(3-AMINOPROPYLAMINO)ETHYLPHOSPHOROTHIOTIC ACID (WR-2721) ON INTESTINAL CRYPT SURVIVAL. II. FISSION NEUTRONS.

Sigdestad CP, Connor AM, Scott RM

Univ. Louisville, Sch. Medicine, 500 South Floyd St., Louisville, KY 40201

Radiat Res; 65(3):430-439 1976

The effect of S-2-(3-aminopropylamino)ethylphosphorothiotic acid (WR-2721) was tested in the jejunum of male C57/Bl6-J mice for its ability to protect against fission neutron irradiation. Lethality, intestinal crypt survival, and DNA synthesizing cellularity were tested. The results showed a dose modification factor (DMF) of 1.6 for lethality in mice treated with WR 2721 prior to fission neutron irradiation. This resulted in the shifting of the dose-mortality probit curve to the right by 149 rad. The crypt survival curve in protected mice had a slope significantly different from unprotected controls. The DMF calculated at 50% crypt survival was 1.3. The dose dependent DNA synthesizing cellularity in the intestine 3 days after irradiation was tested in protected and unprotected animals. WR-2721 protected the intestine from about 120-140 rad of fission neutrons. This resulted in a DMF between 1.4 and 1.5.

108. EFFECT OF CHEMICAL PROTECTORS ON THE RESPONSE OF THE INTESTINE TO ROENTGEN OR FISSION NEUTRON IRRADIATION.

Sigdestad CP, Connor AM, Scott RM

Dept. Radiology, Radiation Center, Univ. Louisville, Louisville, KY 40201

Acta Radiol Ther Phys Biol; 15(5):401-409 1976

The monosodium salt of S-1 (2-hydroxy-3-amino)propylphosphorothionic acid (WR77913) and S-2-aminoethylisothiuronium; Br; HBr (AET) were tested for their protective effects against 4-million electron volt roentgen radiation and fission neutrons in the intestines of male C57/Bl6J mice. The parameters tested were intestinal crypt survival, lethality, and intestinal crypt cellularity. The lethality experiments showed a dose modification factor (DMF) of 1.42 for both drug-tested groups of roentgen-irradiated mice. The DMF's for fission neutron-irradiated mice were 1.48 and 1.2 for WR-77913-and AET-treated animals, respectively. The crypt survival curve for roentgen-irradiated mice treated with AET was parallel to that of the untreated group, but protection from neutron irradiation was less effective. Pretreatment with WR-77913 increased the survival of roentgen- and neutron-irradiated mice significantly, the latter to a lesser exteve. (17 refs)

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C.

Studies with Fractionated Radiation

109. PROTECTION OF MOUSE LUNG BY WR-2721 AFTER FRACTIONATED DOSES OF IRRADIATION

Travis EL, De Luca AM
Department of Experimental Radiotherapy, University of Texas, M. D. Anderson Hospital and Tumor Institute at Houston.
Int J Radiat Oncol Biol Phys; 11(3):521-6 1985

The radioprotective effect of WR-2721 on mouse lung has been studied after single doses, 4 or 7 equal fractions of X rays. Using breathing rate and lethality to measure lung injury up to 1 year after radiation, significant protection against both pneumonitis at 7 months and fibrosis at 12 months was observed using 300 mg/kg of WR-2721. The degree of radioprotection was similar for pneumonitis and fibrosis and was not less after doses per fraction of 4.0 Gy. These data indicate that protection of mouse lung by WR-2721 will not be less in a multifractionated schedule of radiation, at least for doses per fraction greater than 4.0 Gy.

110. PROTECTION OF MOUSE BONE MARROW BY WR-2721 AFTER FRACTIONATED DOSES OF RADIATION (MEETING ABSTRACT)

Travis EL, Fang MZ, Basic I, Milas L, Helbing S
Dept. of Experimental Radiotherapy, M.D. Anderson Hosp., Houston, TX 77030
Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 97, 1985.

The ability of WR-2721 to protect after small doses/fraction has been tested in mouse bone marrow using the exogenous spleen colony assay. Groups of mice were exposed to a range of single doses or 4 equal fractions of radiation given every 6 hr either alone or 30 min after ip injection of WR-2721. Immediately after the last radiation dose the mice were sacrificed, a single cell suspension of bone marrow prepared, and a known number of cells injected iv into recipient mice that had been lethally irradiated 1 day previously with 800 rads TBI. Eight days later spleen colonies were counted. All data were fitted by the LQ model through the origin; if the beta coefficient was not statistically significant, then the data were fitted by linear regression. No cytotoxicity of the WR-2721 could be demonstrated in this schedule. Delaying the excision of the bone marrow by 24 hr after irradiation resulted in decreased survival after all doses, appearing to eliminate the shoulder of the survival curve. Protection was significantly less after fractionated doses than after single doses. These data imply that although the radiation survival curve for bone marrow stem cells is near exponential, ie, has a small beta/alpha ratio, there is sufficient curvature to i2nfluence the protection factor after small doses. Consistent with these findings, there was measurable, although slight, sparing of CFUs with fractionation.

111. RADIOPROTECTION OF A MOUSE TUMOUR BY WR2721 (NSC-296961) WHEN COMBINED WITH SINGLE AND FRACTIONATED RADIATION TREATMENTS (MEETING ABSTRACT)

Hill KP
Physics Division, Ontario Cancer Institute, 500 Sherbourne Street, Toronto, Ontario, M4X 1K9, Canada
Thirty-first Annual Meeting of the Radiation Research Society, February 27-March 3, 1983, San Antonio, Texas. Radiation Research Society 145 pp., 1983.

Experimental studies with the radioprotector WR 2721 [S-2-(3-aminopropylamino) ethylphosphorothioic acid] have suggested that the drug may be more effective in protecting most normal tissues than in protecting tumors. However, many of these studies have examined protection using single large radiation doses when, particularly for tumors, the response may be controlled by hypoxic cells. Since radiation therapy normally employs a series of small dose fractions, when hypoxic cells may be less critical because of reoxygenation, we have examined the extent of protection in a mouse tumor during multiple dose treatments. KHT Sarcomas growing in the legs of C3H mice were treated with single or multiple doses of 100 kVp x-irradiation at 30 minutes after intraperitoneal administration of various concentrations of WR 2721. The tumor cell survival following the treatment was assessed using an in vivo lung colony or in vitro agar colony assay. Initial studies with single radiation doses gave survival curves showing a small amount of protection of the tumors (PF approx 1.4 at a drug dose of 0.5 mg/g body weight, and approx 1.2 at 0.2 mg/g). As a control on the drug efficacy, protection of bone marrow stem cells was also examined using single radiation doses. The survival curves (obtained using a spleen colony assay) indicated considerable protection as has been observed by others (PF approx 3.0 at 0.5 mg/g and approx 1.7 at 0.2 mg/g). When radiation treatment to the tumor was given as a series of 5 Gy fractions, increasing protection was observed as the drug dose was escalated. At a drug dose of 0.2 mg/g body weight the protection factor was approx 1.4. Studies with multiple doses of 3 Gy are still in progress but present results suggest that the level of protection is similar to that obeerved with Gy fractions. (no Refs)

112. RADIOPROTECTION OF TWO MOUSE TUMORS BY WR-2721 IN SINGLE AND FRACTIONATED TREATMENTS

Stewart FA, Rojas A, Denekamp J
Gray Laboratory of the Cancer Research Campaign, Mount Vernon Hospital, Northwood, Middlesex, England.
Int J Radiat Oncol Biol Phys; 9(4):507-13 1983

The radioprotective effect of WR-2721 has been studied in two murine tumors using single doses or five daily fractions. Single dose irradiations of the SA FA resulted in a highly variable radio-protective response. In one experiment large protection factors (1.2-2.5) were obtained, with the greatest protection at low X ray doses. In later experiments with the same tumor, there was little or no radioprotection. The Ca MT was significantly protected against single dose irradiation with both 250 mg/kg and 400 mg/kg of the drug. In a five fraction schedule the extent of radioprotection for CA MT w as greater than with single X ray doses for the same drug dose per fraction. Tumor protection factors from the present work and from the literature are compared with published protection factors for normal tissues. Significant tumor radioprotection is seen in most studies. The data indicate more variability in the extent of tumor protection for a given drug dose than is seen in normal tissues. Tumor protection is often greatest at low X ray doses which may be a result of preferential protection of the better-oxygenated tumor cells.

113. ANTIMETASTATIC EFFECT OF ADETURONE WITH IRRADIATION ON THE LEWIS LUNG CARCINOMA (LCC)

Stoychkov JN, Mircheva JJ
Oncological Res. Inst., Medical Acad., 1156 Sofia, Bulgaria
Dokl Bolg Akad Nauk; 35(11):1603-1605 1982

The influence of the combined action of 137Cs gamma radiation and the radioprotective agent adeturone (AD) on the growth of lung metastases was studied in BDF1 mice with im implanted Lewis lung carcinoma. AD was given ip for 10 days from days 7-11 and from days 14-18 after tumor transplantation, in single doses of 200 mg/kg. Fractionated radiation was administered at a rate of 1.26 Gray (Gy)/min for a

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total dose of 20 Gy; the schedule of irradiations was the same as that for AD, with AD administered 1 hr before irradiation. Results relative to lung metastases 72 hr after end of treatment were recorded as small (diameter up to 1 mm) and large (diameter greater than 1 mm). Antimetastatic effect of treatment was estimated as the percentage inhibition of metastases compared to controls. In untreated control mice there was a total of 56.5 metastases (45.5 small, 11.0 large); in mice given radiation only (1 Gy/day x10) there was a total of 29.0 tumors (25.6 small, 3.4 large). In the mice given both radiation and AD, there was a total of 23.0 tumors (21.3 small, 1.7 large). Total tumor inhibition was 49% for radiation only, 35% for AD only, and 60% for radiation + AD. The degree of inhibition in all three methods of treatment was greatest for large metastases (69%, 47%, and 85%, respectively). The differences both as regards total metastases and degree of inhibition were statistically significant. (10 Refs)

114. RADIOPROTECTION OF MOUSE SKIN BY WR-2721 IN SINGLE AND FRACTIONATED TREATMENTS

Stewart FA, Rojas A
Gray Lab. Cancer Res. Campaign, Mount Vernon Hosp., Northwood, Middlesex HA6 2RN, England
Br J Radiol; 55(649):42-47 1982

The radioprotective action of WR-2721 on mouse skin has been studied using single doses, two and five fractions. Significant radioprotection was observed with 200-500 mg/kg, in animals breathing air or oxygen at the time of irradiation. The degree of radioprotection increased with increasing dose, and was significantly greater in air than in oxygen, especially at low drug doses. Cumulative drug toxicity limited the fractionated treatments to lower drug doses, but the protection observed was similar to that seen with single doses at the same drug levels. The protection factors observed are lower than many published values for skin, and we conclude that a single protection factor cannot yet be stated for any dose of WR-2721. Local tissue oxygenation may account for some of the discrepancies in different studies. (Author abstract) (28 Refs)

115. CHEMICAL PROTECTION AGAINST LONG-TERM EFFECTS OF WHOLE-BODY EXPOSURE OF MICE TO IONIZING RADIATION. III. THE EFFECTS OF FRACTIONATED EXPOSURE TO C57BL MICE

Maisin JR, Gerber GB, Lambiet-Collier M, Mattelin G
Dept. Radiobiology, Euratom and Centre d'Etude de l'Energie Nucleaire, B-2400 Mol, Belgium
Radiat Res; 82(3):487-497 1980

Mice (male, age 4 wk) were given x-rays (50-375 R, whole body, 1/wk, 4 x). Before exposure, one group of mice from each dosage group was treated with a mixture of radioprotectors (glutathione, cysteine, 2-beta-aminoethylisothiouronium-Br-HBr, mercaptoethylamine, and 5-hydroxytryptamine). Other groups served as nonirradiated or irradiated nonprotected controls. Mice surviving 30 days after irradiation were autopsied at the time of natural death. Mean life spans were calculated for each group. The results showed that survival time decreased as the dose increased, but life-shortening (LS) was not a linear function of dose, and LS/R was variable. LS showed a sigmoid dose dependence, and was more pronounced after fractionated doses than after one dose of 650 R. Survival time was prolonged in protected mice compared to nonprotected mice. Protection factors calculated from survival times at a given dose depended on the dose; they were approx 2.9 for doses up to 4 x 100 R, and 1.67 at 4 x 250 R. LS in protected mice after a single exposure was approx the same as LS for fractionated doses, thus protection appeared to be more efficient for fractionated irradiation. The incidence of leukemia increased significantly in protected and nonprotected mice after only 4 x 50 R, and was max (greater than 90%) after 4 x 125 R for nonprotected mice and 70% after 4 x 250 R for protected mice. (24 Refs)

116. EFFECT OF THE RADIOPROTECTIVE DRUGS MEA, DMSO, AND WR-2721 ON TUMOR CONTROL AND SKIN TOLERANCE IN THE RAT

Moulder JE, Lo PS, Fischer JJ
Dept. Therapeutic Radiology, Yale Univ. Sch. Medicine, New Haven, CT 06511
Cancer Treat Rep; 61(5):825-833 1977

Mercaptoethylamine (MEA), dimethylsulfoxide (DMSO), and S-2-(3-aminopropylamino) ethylphosphorothioate (721) were tested for their protective effects against single and fractionated doses of 250-kilovolt x-rays. Acute and late skin reactions and control of BA-1112 rhabdomyosarcoma were examined in both protected and unprotected WAG/Rij rats. All drugs protected skin in both single and fractionated treatment regimens, with MEA giving the most protection and DMSO the least. The dose required to pr oduce a particular skin reaction in 50% of the control animals divided by the dose required to produce the same reaction in 50% of the drug-treated animals (DMF) varied from 0.69-0.85 for various MEA regimens (0.10 mg/g, ip), for 0.86-1.01 from various DMSO regimens (2.25-4.5 mg/g, ip), and from 0.75-0.92 for various WR-2721 regimens (0.10-0.30 mg/g, ip). All three drugs protected tumors against fractionated irradiation, and DMSO and WR-2721 protected tumors against single radiation doses. Only single-fraction treatments of MEA-protected animals showed therapeutically favorable differential protection, with the therapeutic gain factor being significantly greater than 1 (p less than 0.05). (23 Refs)F067

117. PROTECTION OF NORMAL TISSUES BY WR2721 DURING FRACTIONATED IRRADIATION.

Ulley JF, Phillips TL, Kane LJ
Dept. Radiation Medicine, Univ. Kentucky, Lexington, KY 40506
Int J Radiat Oncol Biol Phys; 1(7/8):699-703 1976

To establish the degree of radioprotection when the drug and radiation are administered in single doses and in fractionated doses given with various time intervals, the radioprotective effect of S-2-(3-aminopropylamino)ethyl phosphorothioate (WR2721) was studied in two normal BALB/c Simonson mouse tissues-skin and small intestine-that were given single and fractionated doses of Cs137 radiation. A total of two-thirds of the toxic LD50 of WR2721 could be given before single-dose irradiation. Toxicity increased when the same drug dose was given in two or more fractions before split-dose irradiation: less than one-half of the single drug dose could be administered safely. WR2721 was slightly less protective with fractionated irradiation (DMF = 1.3-1.5) than with single-dose irradiation (DMF = 1.5-1.7) in the skin. The DMF decreased with increased radiation dose in both cases. In the small intestine, WR2721 protection was essentially the same with single-dose irradiation (DMF = 1.6) and fractionated doses (DMF = 1.7). This degree of radioprotection in skin and intestine, in spite of a greatly reduced drug concentration, supports the possibility that WR2721 may be clinically used. (14 refs)

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118. CHEMOPROTECTION AGAINST FRACTIONATED RADIATION EXPOSURES WITH WR-2721: SKIN INJURY.

Echols FS, Yuhas JM
Nuclear Regulatory Commission, Washington, DC 20555
Radiat Res; 66(3):499-504 1976

Analysis of the potential application of WR-2721 [S 2-(3-aminopropylamino)ethylphosphorothioic acid] was extended to radiation therapy by determining the ability of the drug to protect RFM and BALB/c mice against radiation-induced hair loss. The relatively low drug dose used (200 mg/kg) protected mice against hair loss from single exposures by factors of 1.67 and 1.73. The dose necessary to produce a given level of hair loss (ED50) increased with increasing number of fractions. The ED50 increased as N(0.52) and N(0.59) in the two strains of mice when they were not drug-treated, but as N(0.39) and N(0.50) in mice that were drug-treated. Thus, the protective effectiveness of WR-2721 decreased with increasing numbers of fractions, but the drug was still able to give a dose-modifying factor of about 1.23 when the total exposure was given as a series of 9 or 10 fractions. WR-2721 appears to offer the possibility of improving the efficiency of radiotherapy under clinical conditions.

D.
Studies in Tumor Bearing Hosts

1.
Studies with WR-2721

119. BIODISTRIBUTION AND TUMOR RADIOPROTECTION STUDIES WITH THREE PHOSPHOROTHIOATE RADIOPROTECTORS (MEETING ABSTRACT)

Rasey JS, Krohn KA, Menard TW, Spence AM
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Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-16, 1985.

The objective of our study is to measure organ level and cellular level distribution of three phosphorothioate radioprotectors and to correlate this with level of radioprotection and ultimately the metabolic form of the drug. Biodistribution studies have been performed with S-35-WR2721, S-35-WR77913, and S-35- or H-3-WR3689. C3H mice bearing RIF-1, KHT, or C3HBA tumors and BALB/c mice with EMT-6/UW sarcomas were sacrificed 30 min after ip injection. Uptake into blood, normal tissue, and tumors were expressed as percent injected dose/gram (% ID/g). At 30 min high levels of all three drugs were found in submandibular salivary gland (4.02 to 6.95% ID/g) and kidney (3.45 to 6.34% ID/g), with lowest level in brain (0.10 to 0.26% ID/g) and slightly higher levels in skin. At that time, uptake of WR3689 in lung was nearly as great as in kidney, and uptake of WR77913 in gut was nearly as high as kidney levels. At 30 min, uptake in the four tumors ranged from 0.48 to 1.74% ID/g for S-35-WR2721; 0.99 to 2.13% ID/g for S-35-WR77913; and 0.64 to 1.30% ID/g for S-35-WR3689. For the KHT, C3HBA, and EMT-6 tumors, uptake of WR3689 was lower than the other two drugs; this protector also was least effective in crossing the blood brain barrier. Diffusable substance autoradiography with H-3-WR3689 showed homogenous distribution of label in lung and liver but heterogenous distribution in several tissues with high uptake: kidney, small intestine, submandibular gland, and parotid gland. There was no evidence of preferential nuclear localization in any of these tissues. Using in vivo irradiation followed by in vitro clonogenic cell survival of the RIF-1 tumor, the DMF for 400 mg/kg of WR2721 was 1.5 to 1.7. This is being compared to the DMF for WR3689 and WR77913 in this and other tumor systems, to determine if the low uptake of WR3689 in three of the four tumors correlates with low protective efficacy.

120. USE OF WR-2721 WITH TOTAL BODY IRRADIATION IN TREATMENT OF MOUSE LYMPHOMA (MEETING ABSTRACT)

Coia LR, Brown DQ, Mann D
Fox Chase Cancer Center, Philadelphia, PA 19111
Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 42, 1985.

Efficacy of total body irradiation (TBI) in treatment of non-Hodgkin's lymphoma is limited by bone marrow radiosensitivity. WR-2721 has been shown to be an effective chemical protector of the hematopoietic system. In this study, a spontaneous T-cell lymphoma implanted in BALB/c mice was used to determine the effect of WR-2721 on TBI of lymphoma. Mice were randomly assigned to 5 radiation dose groups (0-200 rad TBI) when tumors reached the desired size. The experimental group received the half-max tolerated dose (365 mg/kg) or WR-2721/IP 30 min before 150 rad TBI. Using tumor regrowth delay as an endpoint, WR-2721 was seen not to lessen the delay as would a tumor protector but rather to slightly increase the delay to 216 +/- 9 hr as compared with an expected value of 188 +/- 20 hr based on controls. In a subsequent experiment to determine the effect of WR-2721 alone, the experimental mice received 3 IP injections of WR-2721 (400 mg/kg/day) while the control group received saline. The geometric mean tumor regrowth delay times were 47 +/- 3 hr for the control group compared to 112 +/- 10 hr for the WR-2721 group (p less than 0.001). We conclude that WR-2721 does not give net radiation protection of this lymphoma at the doses studied and has an apparent cytotoxic effect on lymphoma that has not been previously reported.

121. RADIOPROTECTION OF MOUSE SKIN VASCULATURE AND THE RIF-1 FIBROSARCOMA BY WR-2721

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Int J Radiat Oncol Biol Phys; 10(9):1541-4 1984

The degree of radioprotection obtained with WR-2721 is critically dependent upon the oxygen tension of the tissue concerned. It was therefore considered of interest to examine the response of vascular tissue, which would be supposedly well oxygenated, to treatment with WR-2721 plus X rays. The response of this tissue is of interest because of its role in late radiation damage. In addition, for therapeutic gain an agent must protect normal tissue without concomitant tumor protection. However, data on tumor radioprotection have been conflicting and therefore the effect of WR-2721 on an experimental tumor was also tested. Vascular damage was assessed using the fact that tumors grow more slowly in irradiated beds (Tumor Bed Effect). The response of the RIF-1 tumor treated in vivo was measured by in vitro assay of clonogenic survival. WR-2721 (400 mg kg-1) injected 30 minutes before 5 to 30 Gy X rays protected skin stroma by a factor of 1.6. However, WR-2721 given 10 to 60 minutes before 20 Gy X rays to the RIF-1 tumor had either no effect or was protective, according to the method of immobilizing the mice during irradiation. Differences between the ways animals are physically restraine d for tumor irradiation could account for the conflicting data concerning tumor radioprotection with WR-2721.

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122. PROTECTION BY S-2-(3-AMINOPROPYLAMINO)ETHYLPHOSPHOROTHIOIC ACID AGAINST RADIATION-INDUCED LEG CONTRACTURES IN MICE

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Cancer Res; 43(4):1630-1632 1983

S-2-(3-Aminopropylamino)ethylphosphorothioic acid (WR-2721) was shown to provide marked protection against development of radiation-induced leg contractures in C3Hf/Kam mice whose legs were exposed to single doses of gamma-radiation. The radiation doses ranged from 3,300 to 6,200 rad delivered to the right hind thighs from two parallelly opposed 137Cs sources. WR-2721 was given ip 30 min before irradiation. The severity of radiation-induced leg contractures in untreated and WR-2721-treated mice was followed for 342 days after irradiation. The degree of leg contracture in both control and WR-2721-treated mice increased up to 100 days after radiation, when the change stabilized, remaining more or less at the same level to the end of the observation period. During this entire period, the severity of contractures was less in WR-2721-treated mice. The dose-modifying factor for the level of 5 mm reduction in leg extension was 1.5 at 182 days after irradiation. Since WR-2721 did not prevent the radiocurability of 8-mm fibrosarcomas growing in the same legs, these data imply that WR-2721 has a high potential for increasing therapeutic gain when combined with irradiation in the treatment of tumors of an appreciable size. (Author abstract) (19 Refs)

123. STUDIES ON THE RADIOPROTECTIVE EFFECTS OF YM-08310 (= WR-2721) PART 1: RADIOPROTECTIVE EFFECTS OF YM-08310 ON NORMAL AND MALIGNANT TISSUES IN MICE

Tanaka Y, Akagi K, Hasegawa T, Nakazawa M, Harima K, Murata T, Sawada S
Nippon Igaku Hoshasen Gakkai Zasshi; 43(5):700-9 1983

Keywords (MeSH): Animal; English Abstract; Esophagus/radiation effects; Mammary Neoplasms, Experimental/metabolism/*pathology; Mice; Mice, Inbred C57BL; Organothiophosphorus Compounds/*pharmacodynamics; Radiation-Protective Agents/metabolism/*pharmacodynamics; Tissue Distribution; Ethiofos/metabolism/*pharmacodynamics.

124. PROTECTIVE EFFECTS OF WR-2721 AGAINST RADIATION-INDUCED INJURY OF MURINE GUT, TESTIS, LUNG, AND LUNG TUMOR NODULES

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Int J Radiat Oncol Biol Phys; 8(3/4):535-538 1982

The ability of S-2-(3-aminopropylamino) ethylphosphorothioc acid (WR-2721) to protect highly proliferative epitnelium of jejunal crypts, testicular seminiferous tubuli, and low proliferative lung tissue of mice from acute radiation injury and the protection of murine fibrosarcoma microcolonies growi ng in the lung are described. WR-2721 (400 mg/kg, ip) given 30 min before irradiation (1,600 rad) of jejunum and 15 min before irradiation (1,400 rad) of testis, greatly protected jejunal crypts and testicular tubuli from radiation (RT)-induced cell depopulation. The mean number of cryptogenic cells/jejunal circumference of normal mice was approx 24,000, in irradiated mice 6.2 +-1 (standard error) and in WR-treated and irradiated mice 435 +-15. To determine whether WR-2721 can protect against RT-induced enhancement of lung nodules, 400 mg/kg was given to mice 30 min before local thoracic irradiation (LTI), which was followed 1 day later by iv injection with 2 x 10(4) methylcholanthrene-induced fibrosarcoma (FSA) cells. While WR-2721 had no influence on the number of nodules formed 14 days later, RT increased the number of nodules by greater than 4x the control value. Four days after iv injection with 10(4) FSA cells, mice were treated with 400 mg/kg WR-2721 and 30 min later exposed to 1,000 rad LTI. RT greatly reduced the number of FSA nodules in the lung and WR-2721 reduced the tumor-destructive effect of RT. The RT only and RT plus WR-2721 data were significantly different from the nonirradiated control data using the Mann-Whitney U test (p less than 0.001). Using the same test, the number of nodules in the WR-2721 plus RT group differed significantly from the RT only group (P less than 0.004). (19 Refs)

125. PROTECTIVE EFFECTS OF S-2-(3-AMINOPROPYLAMINO)ETHYLPHOSPHOROTHIOIC ACID AGAINST RADIATION DAMAGE OF NORMAL TISSUES AND A FIBROSARCOMA IN MICE

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Dept. Experimental Radiotherapy, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Cancer Res; 42(5):1888-1897 1982

S-2-(3-Aminopropylamino)ethylphosphorothioic acid (WR-2721) was investigated for its protective effect against radiation-produced damage of jejunum, testis, lung, hair follicles, and a fibrosarcoma of C3Hf/Kam mice. Most of these tissues were radioprotected, and the degree of radioprotection depended on the dose of WR-2721 and the time interval between administration of WR-2721 and radiation treatment. WR-2721 increased resistance of jejunal epithelial cells and spermatogenic cells to single doses of gamma-rays by factors of 1.64 and 1.54, respectively. Protection against hair loss was less pronounced; the dose-modifying factor here was 1.24. The radiation-induced acute damage of the lung expressed by the increased formation of tumor nodules in the lung was not decreased by treatment of animals with WR-2721 before radiation. In contrast, WR-2721 augmented the radiation-induced enhancement of metastasis formation in the lung. WR-2721 protected fibrosarcoma micrometastases in the lung against therapeutic effect of radiation by a factor of 1.28. In contrast, this compound has no effect on the therapy of an 8-mm fibrosarcoma growing in the legs of mice. (Author abstract) (29 Refs)

126. EVALUATION OF RADIATION AND WR-2721 IN DOGS WITH SPONTANEOUS TUMORS

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Section Radiology, Sch. Veterinary Medicine, Univ. Pennsylvania, Philadelphia, PA
Radiation Sensitizers: Their Use in the Clinical Management of Cancer. Brady LW, ed. New York, Masson Publishing USA, Inc., Cancer Management, Vol. 5, 321 pp., 1980.

Radioprotection provided to Beagle dog skin by WR-2721 was determined. The possibility of achieving gross response by treating spontaneous tumors with radiation administered in combination with radioprotective levels of WR-2721 was examined. Five dogs undergoing irradiation alone (4 fractions of 10 Grays, for 8 days over a period of 2 wk) developed epilation (5/5 greater than 50% of treated area) and moist desquamation (2/5 greater than 50% of treated area) within the therapy field by day 22 after treatment. Five other dogs were treated with WR-2721 (75 mg/kg, iv) 20 min prior to irradiation. By day 22 post-treatment, 4/5 of the experimental dogs developed epilation involving less than 50% of the treated area and 0/5 developed desquamation. Change in tumor size after treatment was easily evaluated in all five tumor-bearing dogs receiving the 4-fraction and 10-fraction

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(10 radiation-radioprotector treatments given on a 3/wk schedule with a total time of 22 days) protocols. Complete shrinkage of the visible portion of the tumor occurred in 4/5 dogs treated with the 4 radiation-radioprotector fraction protocol and in 1/3 treated with the 10-fraction protocol. Remission periods of greater than 6 mo were observed in 4/9 dogs. Radioprotective effects were noted in dogs treated by either protocol but were most significant in those receiving the four-fraction protocol. Results indicated that WR-2721 has a radioprotective effect; further investigation of potential clinical usefulness is warrented. (12 Refs)

127. THE INFLUENCE OF WR-2721 ON METASTATIC TUMOR SPREAD AFTER IRRADIATION.

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Oak Ridge Natl. Lab., Oak Ridge, Tenn. 37830
IRCS (Cancer); 3(10):27 1975

The effect of the radioprotective drug WR-2721 on local control of the Line 1 alveolar cell carcinoma and on the subsequent survival of tumor-bearing mice after localized radiation was investigated. Graded single doses of radiation (HVL=1.29 mm3) of 3,000-7,000 rads localized to the tumor region were given to 160 tumor-bearing mice 7 days after im injection of 10(6) viable carcinoma cells into the right leg. Half the mice in the experiment were given radiation only and the other half received a single ip injection of WR-2721 just prior to radiation exposure. Animals were considered locally cured if (1) they were locally tumor free and survived 100 days after treatment or (2) died of metastases prior to 100 days but had no evidence of local tumor. Radiation only resulted in a total of 41 cu res, but 43% of locally cured animals had metastases. WR-2721 plus radiation produced 37 local cures, but the percentage of locally cured animals with metastases was reduced to 25%. The data indicate that WR-2721 can protect against metastatic tumor spread after irradiation; the results also suggest that regional normal tissues are important in controlling metastatic spread and that radiation injury can impair the functional integrity of this regional mechanism.

128. RADIOPROTECTION OF TUMOR AND NORMAL TISSUES BY THIOPHOSPHATE COMPOUNDS

Phillips TL, Kane L, Utley JF
Dept. Radiol., Univ. Cal., San Francisco
Cancer; 32(3):528-535 1973

The efficacy of two thiophosphates, S-2-(3-aminopropylamino)ethylphosphorothioate (WR2721) and sodium hydrogen S-(2-aminoethyl)phosphorothioate (WR638) as radioprotective compounds was studied in a wide range of normal and tumor tissues of Swiss Webster and LAF(1) mice. The experiments were carried out with either 300 Kvp x-rays (20 ma, half-value layer 1.6 mm of copper, target surface distance 20-30 cm) or with a self-contained 2,000 Ci 137Cesium irradiator. Dose rates for the 300 Kvp x-rays were in the range of 350-600 rads/min; range for the 137Cesium was 150-350 rads/min. Dose-modifying factors (DMF) were obtained for mouse skin, intestine, bone marrow colony-forming units (CFU), esophagus, lung, and kidney. In addition, DMF were determined for P-388 leukemia, and EMT-6 mouse mammary carcinoma, both assayed in vitro, and for the latter in vivo as well. With the exception of the lung, there is evidence that DMF vary from 1.5 to 3 in normal tissues. In the CFU system treated prior to transplantation, a DMF of 3.0 was observed; when the bone marrow cells were made hypoxic, the DMF was reduced to 1.6. DBA/2 mice exposed to whole body radiation with and without WR2721 revealed a significant difference in the LD50/30 (1,995 and 907 rads, resp), with a DMF of 2.2. Esophageal lethality with WR2721 yielded a DMF of 1.4 at a relatively high endpoint dose (3,807 rads). Whole-body irradiation of mice given 10(6) leukemic cells iv 24 hr prior to irradiation increased mean survival time from 7 to 10 d; although the total body dose deliverable in mice protected by WR2721 was increased by a factor of 2.2, there was no increase in the mean survival time of tumor-bearing animals. When animals bearing EMT-6 mouse tumors were irradiated after receiving WR2721, marked protection occurred in the lower dose range, but at doses of 1,200 rads and higher, the curve for tumors protected with WR2721 parallels the control curve (but shifted above it). This suggests that the compound protects the aerated and well vascularized portion of the tumor, but does not reach the more resistant part. It is not possible to conclude from the experiments whether thiophosphates would be of benefit in clinical radiotherapy. Although the DMF in EMT-6 carcinoma at doses of 500 rads or higher is lower than for many normal tissue endpoints, single, large doses are rarely used clinically; additional studies with multiple small doses in mice are in progress. (17 refs)

129. EFFECT OF RADIOPROTECTIVE DRUGS ON THE THERAPEUTIC RATIO FOR A MOUSE TUMOR SYSTEM

Lowy RO, Baker DG
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Acta Radiol Ther Phys Biol; 12(5):425-433 1973

The radioprotective agents, cysteamine and WR-2721, combined with radiotherapy, improved the therapeutic ratio in treatment of KHT sarcoma sc implanted in C3H/HeJ mice. Tumor control in 50% of the unprotected animals required 5600 R in 2 fractions, while the cysteamine protected animals required 7500 R and the WR-2721 treated animals required 6900 R. The protective action of the agents on the acute skin reaction was investigated through similar fractionated courses of irradiation. The therapeutic ratio, the relation of tumor lethal dose to issue tolerance dose, increased by 30% with cysteamine and 60% with WR-2721. (12 refs)

130. RADIOTHERAPY OF EXPERIMENTAL LUNG TUMORS IN THE PRESENCE AND ABSENCE OF A RADIOPROTECTIVE DRUG, S-2-(3-AMINOPROPYLAMINO)ETHYLPHOSPHOROTHIOIC ACID (WR-2721)

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JNCI; 50(1):69-78 1973

The development of a lung tumor—radiotherapy system in the mouse is described. Alveolar adenomas induced by urethan inj were treated by localized gamma-rays after 6 mo. Methods allowed quantitation of number and size of tumors. WR-2721 (400 mg/kg, ip, approx. 52% of the LD(50)) was admin in aqueous soln. 15 min prior to the beginning of radiation exposure. When admin before exposures as high as 3,000 rads at 68 rads/min, WR-2721 offered no protection to the tumors, but it increased the radiation resistance of the skin and those tissues that determine survival by factors of 1.6—2.1. After 120 d, the radiation LD(50) was 4,523 rads in mice that had received WR-2721, compared to 2,625 rads in those that had not; the drug had increased resistance by a factor of 1.72. When the interval between inj of WR-2721 and the onset of radiation was increased to 90 min, significant protection of the tumor was demonstrated, suggesting not a qualitative difference between tumor and normal tissues in response to the drug, but rather a difference in the time required to respond to its radioprotective action. The authors conclude that WR-2721 offers the possibility of im-

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proving the efficiency of clinical radiation therapy of solid tumors. (14 refs)

131. IMPROVEMENT OF LUNG TUMOR RADIOTHERAPY THROUGH DIFFERENTIAL CHEMOPROTECTION OF NORMAL AND TUMOR TISSUE
Yuhas JM
Biol. Div., Oak Ridge Natl. Lab., Oak Ridge, Tenn.
JNCI; 48(4):1255-1257 1972

The selective radioprotective ability of S-2-(3-aminopropylamino)ethylphosphorothioic acid (AP) for normal tissue was demonstrated in RFM male mice with lung adenomas that had been induced, at the age of 2-3 mo, by a single inj of urethan (1,000 mg/kg). The chest area of the mice was subjected to irradiation (137Cs gamma-ray) 6 mo after tumor induction; AP (400 mg/kg, or 60% of the toxic LD(50) dose) was given, ip, 15 min before irradiation, and tumor size and number were determined 2 mo thereafter in the sacrificed mice. AP offered no radioprotection to the adenomas but doubled the resistance of normal tissues in the lung area. Normal tissue protection was measured by hair loss within 60 d and death within 120 d after irradiation. Exposure to 4,877 R was required to induce hair loss in 50% of the mice following AP treatment, compared with 2,355 R in untreated control mice; treatment with 4,523 R was needed to induce 50% mortality in the mice receiving AP, compared with 2,625 R in untreated controls. Data also suggest that protection of normal tissue is independent of the number of weekly fractions of irradiation. It was concluded that the differential protection of AP is not the product of artificial factors found only in transplanted systems and that it may prove to be a useful adjunct to radiotherapy. (7 refs)

132. DIFFERENTIAL CHEMOPROTECTION OF NORMAL AND MALIGNANT TISSUES
Yuhas JM, Storer JB
Jackson Lab., Bar Harbor, Maine
JNCI; 42(2):331-335 1969

In mice, the admin of S-2-+3-aminopropylamino1 ethylphosphorothioate (WR-2721; 500 mg/kg ip) 15 min before exposure to X-irradiation (1000-4000 r) increased the LD50 within 30 d by 160-170%. Mice bearing transplanted mammary tumors which were irradiated in situ 15 min after inj of WR-2721 were only slightly more resistant (15% increase in the dose required for 50% inhibition of transplantability) than untreated controls. The X-ray dose required to induce skin ulcerations in 50% of the mice was increased 140% by inj of WR-2721. The lack of protective activity in the tumor was probably due in large measure to an availability phenomenon.

2.
Studies with Other Compounds

133. ORGOTEIN AS A RADIOPROTECTOR IN NORMAL TISSUES. EXPERIMENTS ON MOUSE SKIN AND A MURINE ADENOCARCINOMA
Cividalli A, Adami M, De Tomasi F, Palmisano L, Pardini MC, Spano M, Mauro F
Laboratory of Dosimetry and Biophysics, Enea Casaccia, Rome, Italy.
Acta Radiol kOncol; 24(3):273-7 1985

The effects of Orgotein (a superoxide dismutase) on the radiation response of normal and malignant murine tissue in vivo were evaluated. The observations were made on the mouse hind leg bearing, in some cases, an adenocarcinoma. The following irradiation protocols were tested: 1) single dose (e.g., 35 and 53 Gy), 2) conventional fractionation (3 Gy/day, 5 days a week) and 3) multiple fractions per day (2 X 3 Gy/day, 3 h fractionation interval, 5 days a week). Radiation was either delivered alone or preceded by a subcutaneous injection of 20, 100 or 400 mg/kg Orgotein administered 1 or 2 h befo re the beginning of irradiation. No effects of Orgotein on tumor radiation response were detected. A protective effect on normal tissue was observed when radiation was delivered according to aggressive protocols and a relatively high dosage of Orgotein was administered. Furthermore, an accelerated trend of recovery of normal tissue was observed.

134. IN VIVO RADIOPROTECTIVE ACTIVITIES OF DIETHYLDITHIOCARBAMATE (DDC)
Milas L, Hunter N, Ito H, Peters LJ
Department of Experimental Radiotherapy, University of Texas M.D. Anderson Hospital, and Tumor Institute at Houston.
Int J Radiat Oncol Biol Phys; 10(12):2335-43 1984

Studies were performed to determine whether diethyldithiocarbamate (DDC) protects against radiation damage to bone marrow, jejunal crypts, testicular tubules, hair follicles, tissues in the leg responsible for leg contractures, and a fibrosarcoma (FSA) of C3Hf/Kam mice. In most experiments, DDC at a dose of 400 mg/kg or 1000 mg/kg body weight was given i.p. 30 minutes before single doses of gamma radiation. DDC (1000 mg/kg) given 30 minutes before whole-body irradiation protected hematopoietic stem cells by a factor (PF) of 1.59, as assessed by the LD50/30 assay, and by PFs of 1.32-1.55, as assessed by the endogenous spleen colony assay. A dose of 400 mg/kg DDC was less effective. Protection was also significant against hair loss and leg contractures; PFs produced by 1000 mg/kg DDC were 1.44 and 1.38-1.51, respectively. Jejunum was protected by 400 mg/kg DDC (PF = 1.2), but not by 1000 mg/kg. The opposite was observed with testis: 1000 mg/kg was protective (PF = 1.2), but not 400 mg/kg. DDC also protected the FSa tumor, either as lung micrometastases or as a solitary tumor in the leg. Both 400 mg/kg and 1000 mg/kg DDC protected 4 day-old micrometastases by a PF of approximately 1.1. DDC at a dose of 1000 mg/kg protected 8 mm leg tumors by a PF of 1.24 at the TCD50 level. Therefore, DDC protected both normal tissues and FSA, but the degree of protection varied greatly. A therapeutic gain was achieved in some instances.

135. AN IN VIVO STUDY OF THE RADIOPROTECTIVE EFFECT OF DIETHYLDITHIOCARBAMATE (DDC)
Evans RG, Engel CR, Wheatley CL, Nielsen JR, Ciborowski LJ
Fricke Radiobiology Research Laboratories Mayo Clinic and Mayo Foundation Rochester, MN.
Int J Radiat Oncol Biol Phys; 9(11):1635-40 1983

We have recently shown that diethyldithiocarbamate (DDC) protects plateau-phase cultures of mammalian cells from radiation. Experiments in vivo have extended our knowledge of the radioprotective properties of DDC and show that the LD50/30 in mice is increased from 780 rad to approximately 1400 rad when non-toxic concentrations of DDC are present prior to the irradiation. When DDC is present during irradiation, the pattern of death of the mice is similar to that seen in the absence of the drug an d is quite different from that seen in animals dying of a gastrointestinal syndrome (LD50/7 congruent to 1700 rad). To confirm that the LD50/30 data represent bone marrow protection by DDC, we performed bone marrow CFUS assays with and without the presence of DDC, at the time of in vivo irradiation. The DO of the CFUS is increased from 80 rad in the control animals to 120 rad in the animals that have been pretreated with DDC. In experiments using 35S-labelled DDC, the tissue distribution of the drug in tumor-bearing mice indicates a preferential uptake of DDC in kidney, lung and bone marrow

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compared to tumor tissue. Based on data from both in vitro and in vivo studies, we believe that DDC shows promise as a radioprotective agent and should be considered for clinical trials.

136. TOXICITY AND RADIATION PROTECTIVE EFFECT OF WR-77913 IN BALB/C MICE

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Acta Radiol Oncol Radiat Phys Biol; 21(5):319-323 1982

The toxicity and radiation protective effect obtained by ip injection of sodium hydrogen S-(3-amino-2-hydroxypropyl) phosphorothioate (WR-77913) have been investigated in BALB/c mice. The toxic LD50/30 was 3,574 mg/kg. When WR-77913 was given 30 min before whole body irradiation adequate protection was observed against bone marrow and gut death. Dose modifying factors of 1.91 and 1.76 for bone marrow and 1.95 and 1.80 for gut death were obtained with drug doses roughly equivalent to one half and one quarter of the maximum tolerable doses (MTD). No protective effect was observed against central nervous system injury. Preliminary experiments with EMT6 tumor show limited tumor protection with a dose of WR-77913 equivalent to 70 percent of the MTD. Because of its low toxicity, adequate bone marrow and gut protection at doses equivalent to one quarter MTD and limited protection of the EMT6 tumor, WR-77913 deserves further investigation to determine its value in multiple drug dose regimens and its capability to protect other normal tissues. (Author abstract) (23 Refs)

137. COMBINED TREATMENT OF THE LEWIS LUNG CARCINOMA WITH TOTAL RADIOTHERAPY AND ADETURONE

Mircheva JJ, Fantev TP, Stoychkov JN
Oncology Res. Inst., Medical Acad., 1156 Sofia, Bulgaria
Dokl Bolg Akad Nauk; 35(11):1607-1610 1982

The possibility of increasing the effectiveness of 137Cs whole body gamma radiation with the use of a radioprotective agent, adeturone (AD), was studied in BDF1 mice of both sexes implanted with Lewis lung carcinoma (LLC). AD in single doses (mg/kg/day x 10) of 200, 250 and 300 was administered ip 1 hr before irradiation. Mice received radiation following the schedule for AD, in total doses of 5-20 Gray (Gy). Therapeutic effect was estimated 24 hr after end of treatment as percentage tumor wt in hibition (TWI). AD alone in doses of 200, 250 and 300 mg brought about a TWI of 50, 48, and 45%, respectively. With a total dose of 5 Gy radiation only (0.5 Gy x 10), TWI was 46%; after total doses of 10 and 20 Gy, TWI was 61 and 73%, respectively. After a total dose of 5 Gy plus total doses of 2,000 and 2,500 mg AD, TWI was 60 and 59%, respectively. After a total dose of 10 Gy and 2,000 mg AD, TWI was 81% but 2/8 mice died. After a total dose of 10 Gy and 2,500 and 3,000 mg AD, TWI was 80 and 69%, respectively, with no deaths. After a total dose of 20 Gy and 2,500 mg AD, TWI was 78% but 2/8 mice died. It is concluded that AD increases the effectiveness of total radiotherapy of LLC, as well as reducing the general toxic effect of ionizing radiation. (8 Refs)

138. RADIOPROTECTION OF NORMAL AND MALIGNANT TISSUE IN THE MOUSE BY DIETHYLAMINORESERPINE

Lebnert S, Fisher G, Methot G
Dept. Radiation Oncology, McGill Univ., Montreal, Canada
Int J Radiat Biol; 40(1):63-73 1981

The protective effect of pre-irradiation of diethylaminoreserpine (DL-152) for normal and malignant tissues in the mouse has been investigated. Dose modifying factors (DMFs) obtained for normal tissue ranged from 1.0 for bone marrow CFUs to more than 1.8 for skin. The DMFs for two transplantable tumors investigated were 1.0 for the EMT6 adenocarcinoma and 1.70 for the KHT fibrosarcoma (at a surviving fraction of 0.1). Acutely hypoxic KHT tumors were protected to a slightly lesser extent than were aerated tumors. For the KHT tumor, the number of clonogenic cells recovered from non-irradiated tumors 1 hr after DL-152 injection was reduced to 60% of the number recovered from saline-injected controls, while, if DL-152 injected mice were acutely hypoxic at the time of sacrifice, the number of clonogenic cells was further reduced. The survival of non-irradiated EMT6 tumor cells was unaffected by DL-152 injection prior to sacrifice. (Author abstract) (13 Refs)

139. THE EFFECT OF SEVERAL DIFFERENT ANAESTHETICS ON THE BLOOD PRESSURE AND HEART RATE OF THE MOUSE AND ON THE RADIATION RESPONSE OF THE MOUSE SARCOMA RIF-1

Cullen BM, Walker HC
MRC Cyclotron Unit, Hammersmith Hospital, London, U.K.
Int J Radiat Biol; 48(5):761-71 1985

Several anaesthetics were tested with mice to study: (a) their ability to immobilize the animal; (b) their effect on blood pressure and heart rate; and (c) their effect on the response to X-irradiation of the mouse sarcoma RIF-1. All anaesthetics which produced adequate immobilization also caused a fall in blood pressure and some radioprotection of tumour cells. Physical restraint of the tumour-bearing leg of an unanaesthetized mouse also caused radioprotection of the tumour cells.

140. LOCAL ANAESTHETICS AS HYPOXIC RADIOSENSITIZERS, OXIC RADIOPROTECTORS AND POTENTIATORS OF HYPERTHERMIC KILLING IN MAMMALIAN CELLS

Yau TM, Kim SC
Dept. Radiology, Case Western Reserve Univ., Cleveland, OH, 44106
Br J Radiol; 53(631):687-692 1980

Local anesthetics with well-known pharmacology are found to radiosensitize hypoxic and radioprotect oxic murine L5178Y cells. Under the specific experimental conditions, radiation-modifying effects exerted by local anesthetics are dose-dependent. It appears that in order that the drugs should act as oxic radioprotectors or as hypoxic radiosensitizers, the agent must be present during the period of irradiation. Local anesthetics are also found to potentiate the hyperthermic killing of cells. The possibility of applying compounds with such dual radiation-modifying properties plus hyperthermia-potentiating capacity to enhance the therapeutic gains in tumor therapy is briefly discussed. (Author abstract) (40 Refs)

141. DIFFERENTIAL EFFECT OF CYCLOHEXIMIDE ON NORMAL TISSUE TOLERANCE AND TUMOR CONTROL IN IRRADIATED RATS

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Int J Radiat Oncol Biol Phys; 10(7):1073-8 1984

The effect of the protein synthesis inhibitor cycloheximide (CHM) on normal tissue tolerance and tumor control in the rat following single doses of radiation has been studied. We have previously shown that the drug protects against skin damage when administered prior to irradiation of the hind limbs. It does not protect against six-month lethality when given prior to irradiation of the kidneys. In the present studies protection of rat bone marrow as evidenced by 30-day

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lethality was observed when CHM was given prior to whole-body irradiation. When CHM was given to rats bearing the BA1112 tumor, it had no protective effect on radiocurability. Therapeutically favorable differential protection of rapidly proliferating normal tissue over tumor can be achieved when CHM is administered prior to single radiation doses in the rat. This effect is most likely due to inhibition of protein synthesis and resultant interruption of the cell cycle in proliferating normal tissue. Further studies are required to determine the clinical applicability of CHM.

III.

MECHANISMS OF ACTION OF RADIOPROTECTORS

A.

Effects on Cell Cycle, Chromosomes, and Nucleic Acids

142. INDUCTION OF SISTER-CHROMATID EXCHANGES BY N-NITROSOCIMETIDINE IN CULTURED HUMAN LYMPHOCYTES AND ITS INHIBITION BY CHEMICAL COMPOUNDS

Inoue K, Shibata T, Kosaka H, Uozumi M, Tsuda S, Abe T
Laboratory of Food Microbiology, Osaka Prefectural Institute of Public Health, Japan.
Mutat Res; 156(1-2):117-21 1985

The effect of nitrosocimetidine (NC) on the frequency of sister-chromatid exchanges (SCEs) in human lymphocytes has been studied. The frequency of SCEs induced by a 1-h exposure to 2.6 X 10(-4) M NC was 4-fold greater than that in the solvent control. A 72-h exposure to NC had a similar dose-related effect. We also examined the effect of the sulfhydryl compounds cysteine, cysteamine, cystamine and glutathione, the reducing agent dithionite, and vitamins C and E on the NC-induced SCEs. None of these compounds induced SCEs. Cysteine, cysteamine, and cystamine significantly reduced the number of NC-induced SCEs, and the others did not.

143. DNA REPAIR SYNTHESIS AND REJOINING OF STRAND BREAKS IS FAVOURABLY AFFECTED BY WR-2721 IN PREFERENCE TO CYSTEAMINE (MEETING ABSTRACT)

Riklis E, Prager A, Green M, Minsberg M
Radiobiology Dept., Nuclear Res. Center-Negev, Beer-Sheva, Israel
Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-1, 1985.

It has been previously established by us that: (1) The radioprotectors WR-2721 and Cysteamine, following exposure to gamma radiation, increase the survival of mammalian cells in culture, and (2) WR-2721 increases cellular DNA repair capacity as measured by labeled thymidine incorporation into PUVA-treated cells. In order to determine the mechanism of action of WR-2721, its effects on specific damage types and specific repair systems should be identified. Of the various damage and repair events, the following have so far been studied: (1) DNA strand break formation and repair-rejoining following gamma radiation, and (2) DNA strand break formation and repair following BUdR + fluorescent light exposure. The effects of SR-2721, cysteamine (MEA) and sodium dithionite on the formation and repair of DNA strand breaks in gamma irradiated cells were measured by alkaline sucrose gradients. All three compounds caused a reduction in the number of strand breaks formed. Only WR-2721 was effective in increasing the rejoining of strand breaks. This was established by adding each of the compounds only after the exposure to radiation. In preventing damage by BUdR and light exposure, WR-2721 and MEA were slightly effective while Na-dithionite was not. None of the compounds was effective in increasing repair of BUdR + light strand breaks, but MEA and Na-dithionite actually inhibited the rejoining of strand breaks. Various approaches to combined modality for radiotherapy indicate the central role of DNA repair in determining the possibility of modification of cellular response. The most effective radioprotector, WR-2721, owes its effectiveness to the fact that it increases DNA repair capacity and the rejoining of DNA strand breaks. The general conclusions are: (1) Only WR-2721 of the compounds studied is effective as a radioprotector by both prevention of damage and increase of repair; (2) The modes of action of WR-2721 and of cysteamine are different; (3) Anoxic conditions, as caused by Na-dithionite, do not always support cellular resistance. When resistance is a result of repair, anoxia causes reduced repair and therefore increased damage. Responses to radioprotective compounds a re summarized in a table.

144. PROTECTION AGAINST RADIATION INDUCED CHROMOSOME INJURY BY SULFHYDRYL COMPOUNDS

Gupta R, Uma Devi P
Department of Zoology, University of Rajasthan, Jaipur, India.
Acta Radiol Oncol; 24(5):419-25 1985

The radiation induced changes in a critically radiation-sensitive tissue, bone marrow of Swiss albino mice and its modification by two sulfhydryl compounds, MPG and WR-2721, were studied cytogenetically after whole body exposure to 0.5, 1.5, 3.0, 4.5 and 6.0 Gy of 60Co gamma radiation. The changes in the structural arrangements of chromosomes in the bone marrow were studied at various post-irradiation times from 1 to 28 days. Both the control (irradiated) and experimental (drug + irradiation) animals showed qualitatively similar types of aberrations; the severity of lesions increased with the radiation dose. The maximum damage in all the groups was seen on day 1, post-irradiation. Both the drugs afforded better protection at lower doses of exposure, their effectiveness decreasing with an increasing radiation dose. Of the two drugs, WR-2721 was more effective than MPG against initial aberration yield but the former, at the present drug dose, showed some toxic effect at the later post-irradiation intervals (2 weeks onward) as manifested by an increase in the chromatid breaks and polyploidy.

145. RADIOPROTECTION AND DNA REPAIR: II. THE EFFECT OF WR-2721 AND CYSTEAMINE ON FORMATION AND REPAIR OF DNA STRAND BREAKS (MEETING ABSTRACT)

Green M, Prager A, Riklis E
Radiobiology Dept., Nuclear Res. Center-Negev, Beer-Sheva, Israel
International Conference on Mechanisms of DNA Damage and Repair. Implications for Carcinogenesis and Risk Assessment. Poster Sessions. June 2-7, 1985, Gaithersburg, Maryland, 1985.

The effect of the radioprotective compounds on the formation of damage was separated from its repair by having the protectors present at different times: before, during, or only after the exposure, the last being the time of repair. Measuring 3H-thymidine incorporation into PUVA-treated mammalian cells (a treatment which fully inhibits normal DNA synthesis) gave an indication of DNA repair synthesis. WR-2721 causes increased repair when added after exposure to gamma radiation. When the drug is present during exposure only, and is immediately removed following exposure, the level of repair activity is lower than without the drug, indicating a reduction in damage, but when present both during and after

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exposure, the outcome is a combination of reduced damage and increased repair. Cysteamine did not increase the repair when added after the exposure, but showed its effect as a radical scavenger by reducing the damage when present during irradiation. These observations are explained in the more specific experiments on the effects of WR-2721, cysteamine and the general reducing agent sodium dithionite on the formation and repair of single strand breaks in DNA; sedimentation of lysed cells was performed at 0 C for 90 min at 36,000 rpm. All three compounds were shown to exert a protective action by reducing the number of strand breaks when present during exposure to gamma radiation. WR-2721 was, however, the only compound which brought about a reduction in the number of strand breaks when added only after the exposure to radiation, during the 20 min rejoining, ie repair period. The effect of cysteamine and WR-2721 on rejoining is shown in a figure. WR-2721 is therefore a radioprotector with potential for both prophylactic and therapeutic action.

146. THE EFFECTS OF WR-2721 ON THE CELL SURVIVAL AND DNA SEDIMENTATION IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES AGAINST GAMMA RADIATION (MEETING ABSTRACT)

Fu YK
Inst. of Nuclear Energy Res., P.O. Box 3-27 Lung-Tan, Taiwan, R.O.C.
Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 43, 1985.

The radioprotective agent, WR-2721, was studied for its cytotoxicity and radioprotection on human peripheral blood lymphocytes. The relative radiosensitivities of lymphocyte populations and enriched T and B-cell populations following in vitro gamma-irradiation (at 0-8 Gy) were determined. Trypan blue dye exclusion method was used to determine cell survival and ethidium bromide-DNA complex sucrose density gradient centrifugation including spectrophotometry was used to measure DNA damage, respectively. There is no effect on cell membrane integrity up to drug concentrations below 1500 ug/ml for 2 hr treatment. In concentration of 5000 ug/ml, the resistance of cells to drug decreases to 60% in 2 hr treatment, but DNA damage has not been detected. The dose reduction factor (DRF), obtained from cell survival of drug treatment 30 min before irradiation, is correlated to drug concentration. The DRF values for 1000 and 1500 ug/ml treatments are 1.33 nd 1.19 respectively. In comparison with our other results on DRF values of WR-2721 on NIH mice bone marrow chromosome aberration and V79 cell survival are 2.88 and 1.17 respectively, the results show that WR-2721 has more radioprotective effects in vivo than in vitro. On the other hand, WR-2721 shows only slight radioprotective effects on DNA sedimentation ratio.

147. EQUILIBRIUM DIALYSIS STUDIES OF WR-33278 AND WR-1065 BINDING TO CALF THYMUS DNA (MEETING ABSTRACT)

Smoluk GD, Fahey RC, Ward JF
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Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 44, 1985.

Radioprotection by WR-2721, S-2-(3-aminopropylamino)ethyl phosphorothioate, is thought to involve its corresponding thiol (WR-1065) or symmetrical disulfide (WR-33278). It has been suggested that these metabolites concentrate close to the DNA target molecule. As one test of this hypothesis we measured the ability of these metabolites to bind or concentrate with DNA in vitro in order to achieve a high local concentration. The binding of WR-33278 (0.50-0.4mM) to calf thymus DNA (6mM, with respect to phosphate) was determined at 50, 100, and 150mM-KCl in 1mM-Tris, pH 7.0, by equilibrium dialysis. Drug levels were analyzed by derivatization with monobromobimane, and quantitated by fluorescence HPLC, (samples were reduced with dithiothreitol prior to analysis). Dissociation constants, (Kd = (unbound DNA phosphate) (unbound WR-33278)/(bound WR-33278)), under these conditions were found to be in the range of 0.5-6 mM. Preliminary studies with WR-1065 indicate that it also binds to DNA but with larger Kd values. Results suggest that concentration of WR-33278 and WR-1065 by electrostatic attraction to DNA phosphate can be a significant factor in the mechanism of radioprotection by WR-2721.

148. THE EFFECTS OF THE RADIOPROTECTOR WR1065 ON RADIATION-INDUCED CELL KILLING, MUTAGENESIS, DNA DAMAGE AND REPAIR IN V79 CELLS (MEETING ABSTRACT)

Grdina DJ, Nagy B, Dale PJ, Angerman JM
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International Conference on Mechanisms of DNA Damage and Repair. Implications for Carcinogenesis and Risk Assessment. Poster Sessions. June 2-7, 1985, Gaithersburg, Maryland, 1985.

WR1065 [N-(2-mercaptoethyl)-1,3-diaminopropane] protects against radiation-induced cell killing and mutagenesis at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus in V79 cells. Formation of single-strand breaks (SSBs) in DNA is reduced by the presence of WR1065 during irradiation, but subsequent postradiation rejoining processes are inhibited by this agent. Four treatment protocols were followed: (a) cells were exposed to various doses of radiation only; (b) the radioprotector WR1065, always made up as a 1 M stock solution in phosphate buffered saline (Dulbecco's PBS: GIBCO), was added to cell cultures 30 min prior to irradiation to give a final concentration of 4 mM (eg, a concentration empirically determined to be nontoxic while offering max protection) and was allowed to remain only until the end of irradiation; (c) WR1065 was added immediately after irradiation and allowed to remain for 3 h; and (d) WR1065 was added 3 h after irradiation and allowed to remain for 3 h. Following treatment, cells were prepared and plated according to standard methods. Mutation frequencies were determined with a 6-day expression time. Background mutation frequencies ranged from 3 to 25 mutants per 10(6) cells, and all radiation-induced mutation frequencies were corrected for the appropriate background mutation frequencies. WR1065 effectively protected against cell death only if present during irradiation, eg, a dose modification factor (DMF) of 1.9. No protective effect was observed if WR1065 was added within 5 min after irradiation or 3 h later, eg, DMFs of 1.0 and 1.1, respectively. WR1065 effectively reduced radiation-induced mutations regardless of when it was administered. Following a dose of 1000 rad of 60Co gamma-rays, the mutation frequencies observed per 10(6) survivors were 77 +/- 8, 27 +/- 6, 42 +/- 7, and 42 +/- 7 for radiation only, and WR1065 present during, immediately after, or 3 h after irradiation. Damage and repair of SSB in DNA following a dose of 1000 rad was measured by using alkaline elution. WR1065 did not induce SSB in unirradiated control cells following exposure times of up to 180 min. If present during irradiation, WR1065 significantly protected against the formation of SSB. When WR1065 was added immediately following irradiation and repair was monitored, the protector inhibited the rate of rejoining of SSB by about a factor of 3. It may be that this reduction in the rate of SSB rejoining is accompanied in some manner by a greater fidelity of repair leading to a reduction in mutagenesis. Regardless of

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the mechanisms involved, these data suggest that although a segment of radiation-induced damage leading to reproductive death cannot be modulated through the postirradiation action of WR1065, processes leading to the fixation of gross genetic damage and mutation induction in surviving cells can be effectively altered and interfered with leading to a marked reduction in mutation frequency.

149. WR1065 PROTECTION AGAINST RADIATION-INDUCED MUTATIONS AT THE HGPRT LOCUS IN V79 CELLS (MEETING ABSTRACT)

Nagy B, Grdina D, Hill C, Dale P
Argonne Natl. Lab., Argonne, IL 60439
Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 98, 1985.

WR1065 protects against radiation-induced cell killing and mutagenesis at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus in V79 Chinese hamster lung fibroblast cells. At a concentration of 4mM, WR1065 effectively protected against cell death only if present during irradiation, eg, a dose modification factor (DMF) of 1.9. No protective effect was observed if WR1065 was added within 5 min after irradiation or 3 hr later, eg, DMFs of 1.0 and 1.1, respectively. In contrast, WR1065 effectively reduced radiation-induced mutations regardless of when it was administered. Following a dose of 1000 rad of 60Co gamma rays, the mutation frequencies observed per 10(6) were 77 +/- 8, 27 +/- 6, 42 +/- 7, and 42 +/- 7 for radiation only, and WR1065 present during, immediately after, or 3 hr after irradiation. These data suggest that although a segment of radiation-induced damage leading to reproductive death cannot be modulated through the post-irradiation action of WR1065, processes leading to the fixation of gross genetic damage and mutation induction in surviving cells can be effectively altered and interfered with leading to a marked reduction in mutation frequency.

150. SUPPRESSION OF RADIATION MUTAGENESIS BY DACTINOMYCIN IN CHINESE HAMSTER CELLS (MEETING ABSTRACT)

Tokita N, Carpenter SG, Chen DJ, MacInnes MA, Raju MR
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Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 42, 1985.

Dactinomycin (AMD) suppression of radiation mutagenesis was investigated using an in vitro mutation assay (6-thioguanine resistance) in Chinese hamster ovary cells. Cells are exposed to acute single doses of x-rays followed by a 1 hr-treatment with 0.1 of 1 ug/ml AMD. The cell survival curves plotted as a function of x-ray dose were similar for radiation alone and radiation plus AMD. The results suggest that AMD treatment was only slightly mutagenic, however, when given immediately after irradiation, it suppressed radiation mutagenesis at higher x-ray dose regions (below 10% survival levels). Higher AMD concentrations appeared more suppressive than lower concentrations. Dose-response data analyzed based on Poisson distribution models suggest the stochastic dependence of x-ray mutagenesis and AMD cytotoxicity.

151. THE RADIOPROTECTOR WR1065 REDUCES RADIATION-INDUCED MUTATIONS AT THE HYPOXANTHINE-GUANINE PHOSPHORIBOSYL TRANSFERASE LOCUS IN V79 CELLS

Grdina DJ, Nagy B, Hill CK, Wells RL, Peraino C
Radiation Carcinogenesis Group, Argonne National Laboratory, IL 60439.
Carcinogenesis; 6(6):929-31 1985

N-(2-mercaptoethyl)-1,3-diaminopropane (WR1065) protects against radiation-induced cell killing and mutagenesis at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus in V79 Chinese hamster lung fibroblast cells. At a concentration of 4 mM, WR1065 was found to be effective in protecting against radiation-induced cell lethality only if present during irradiation, e.g., a dose modification factor (DMF) of 1.9. No protective effect was observed if the protector was added within 5 min after irradiation or 3 h later, e.g., DMFs of 1.0 and 1.1, respectively. The effect of WR1065 on radiation-induced mutation, expressed as resistance to the cytotoxic purine analogue 6-thioguanine (HGPRT), was also investigated. In contrast to the treatment-schedule dependence for protection by WR1065 against cell killing, this agent was effective in reducing radiation-induced mutations regardless of when it was administered. Following a dose of 10 Gy of 60Co gamma-rays, the mutation frequencies observed per 10(6) survivors were 77 +/- 8, 27 +/- 6, 42 +/- 7, and 42 +/- 7 for radiation only, and WR1065 present during, immediately after, or 3 h after irradiation. These data suggest that although a segment of radiation-induced damage leading to reproductive death cannot be modulated through the postirradiation action of WR1065, processes leading to the fixation of gross genetic damage and mu tation induction in surviving cells can be effectively altered and interfered with leading to a marked reduction in mutation frequency.

152. MODIFICATION OF CF-252 LETHALITY TO HUMAN CELLS BY CAFFEINE AND DMSO (MEETING ABSTRACT)

Schroy CB, Goud SN, Magura C, Feola JM, Maruyama Y
Radiation Medicine, Univ. of Kentucky, Lexington, KY
International Neutron Therapy Workshop. April 21-24, 1985, Lexington, Kentucky, abstract R2, 1985.

Potentially-lethal damage (PLD) repair is often measured in one of two ways: (1) releasing cells from plateau phase at various times after irradiation, and (2) having a modifier like caffeine in the medium during the post-irradiation repair period. Although these assays are probably testing different cellular phenomena, dose rate and geometry mitigated against our doing the first assay for PLD. The same geometry was used as for our other work. Suspended log-phase human T-1E cells were placed in a 3.2-cm diameter cylindrical array of 24 Cf-252 sources totalling 320 ug in a Lucite phantom. The dose rates at the center line were approx 62 cGy/h of gamma rays and 135 cGy/h of neutrons. Aliquots were withdrawn periodically and plated. The absence of a large shoulder and the almost purely exponential shape on the T-1E survival curve (unlike V79-S171) allowed 1% survival to be achieved in 1.7h. When 2mM caffeine was present for 48h post-irradiation the dose necessary for 10% survival was reduced by about one-third, indicating that significant amounts of PLD exist after Cf-252 exposure. This is commensurate with previous findings by Schroy et al using fast neutrons at the Naval Research Laboratory (Radiat Res 84:353,1980). In a similar radioprotection experiment using 2M DMSO, the dose necessary for 10% survival was increased by 50%, indicating that scavengable free radicals play an important role in Cf-252 lethality. Such protection was observed for heavy ions by Chapman et al (Radiat Environ Biophys 16:29, 1979). (2 Refs)

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153. MODIFICATION BY DEXAMETHASONE OF RADIATION RESPONSE OF IN VITRO CULTURED CELLS

Bruck WA, Williams M, McNaney D, Milas L, Peters LJ, Weichselbaum RR
Department of Experimental Radiotherapy, University of Texas M. D. Anderson Hospital and Tumor Institute at Houston.
Int J Radiat Oncol Biol Phys; 10(11):2113-7 1984

Because of the potential clinical significance of the report that dexamethasone is a radioprotector of Chinese hamster V-79 cells, the effect of dexamethasone treatment on the radiosensitivity of five other cultured mammalian cell lines (including two human cell lines) was tested and preliminary investigations into the mechanism of protection of V-79 cells were undertaken. In agreement with the published results of others, we found that treatment of V-79 cells with dexamethasone results in a 1.3-fold increase in D0. Conversely, dexamethasone had no effect on the radiosensitivity of Chinese ham ster ovary cells, murine fibrosarcoma, rat glioma cells, human diploid fibroblasts, or human mammary carcinoma cells. To study the mechanism of the radioprotective effect of dexamethasone on V-79 cells, the cell cycle was examined. Dexamethasone treatment causes a change in cell cycle distribution in V-79 cells, resulting in a dose-dependent reduced fraction of S-phase and an increased fraction of G1- and G2 + M-phase cells. However, these kinetic changes cannot explain the observed radioprotection of asynchronous populations, since purified G1 cells are more radiosensitive. Furthermore, cells synchronized in G1 by centrifugal elutriation were shown to be protected by dexamethasone to the same extent as was the unsorted population, thereby ruling out the mechanism of protection being a redistribution in the cell cycle.

154. EFFECT OF L-CYSTEINE ON THE DOSE-EFFECT RELATIONSHIP FOR CHROMOSOME ABERRATIONS IN IRRADIATED HUMAN LYMPHOCYTES

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Int J Radiat Biol; 42(2):211-214 1982

The aberration yields observed in irradiated human whole-blood G0 lymphocytes, with or without L-cysteine added 30 min before irradiation, were compared. Fewer dicentrics and acentrics were observed when cells were treated with L-cysteine before irradiation. The decrease in aberration yields were even more decreased at higher L-cysteine dosages. It is generally accepted that dose-effect relations for radiation-induced chromosome aberrations, with low linear energy transfer radiations, are nonlinear and can be described by a linear-quadratic function of the type (alphaD + betaD(2)). When cells were pretreated with L-cysteine, beta was not significantly different from zero, and the dose-effect relationship was linear. Assuming the possibility of beta = 0 in the case of L-cysteine protection, at least three interpretations are possible: either the part of the aberration yield described by the quadratic component corresponds to the exchange aberrations formed from primary lesions induced by radiation indirectly; or the deactivation of primary lesions is in general in competition with lesion fixation which is radical-dependent; or L-cysteine molecules bind to the DNA and thus prevent the formation of primary lesions, which, remaining unrepaired, may lead to the formation of aberrations which are in their nature different from lesions leading to the aberrations described by the linear component of the dose-effect relationship. (6 Refs)

155. SEMICONSERVATIVE AND UNSCHEDULED DNA-SYNTHESIS OF RAT THYMOCYTES UNDER THE INFLUENCE OF SOME RADIOPROTECTING AND RADIOSENSITIZING AGENTS

Tempel K, Wulffius-Koch M, Winkle J, Schermold I
Koniginstr. 16, D-8000 Munchen 22, W. Germany
Strahlentherapie; 158(2):112-122 1982

The effects of aminoethylisothiuroniumbromide (AET), cysteamine (CY-A), cysteine (CY-E), glutathione (GLU), mercaptoethanol (MA), mercaptopropionylglycine (MPG), N-ethylmaleimide (NEM), metronidazole (MNA), nitroacetophenone (NAP), nitrofurazone (NFA), arabinofuranosylcytosine (araC), fluorouracil (FU), adriamycin (AM), ethidium bromide (E), bleomycin (BM), and diethyldiethiocarbamate (DDC) on the semiconservative and unscheduled incorporation of 3H-thymidine into the DNA were tested on rat thymocytes in vitro. DNA damage has been measured using the hydroxylapatite system. Unscheduled DNA synthesis was induced by UV-light and/or x-irradiation. The semiconservative DNA synthesis was inhibited by the above substances, with the exception of MA and MPG. Aminothioles, NAP, NFA, and BM enhanced, while araC, FU, AM, E, and DDC diminished unscheduled DNA synthesis. After alkaline unwinding, the duplex form of DNA decreased under the influence of CY-A, CY-E, GLU, MPG, NEM, NAP, NFA, araC, FU, AM, E, and BM. It is suggested that stimulation of unscheduled DNA synthesis combined with a transient decrease of semiconservative DNA synthesis will amplify the DNA repair capacity of thymocytes, whereas radiation damage may be intensified by araC, FU, AM, E, and DDC, at least partly, through inhibition of unscheduled DNA synthesis. With respect to the action of NAP, NFA, and BM, DNA repair may be concerned in a more indirect manner. (Author abstract) (80 Refs)

156. CYSTEAMINE PROTECTION OF SCES INDUCED BY UV AND FLUORESCENT LIGHT

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Mutat Res; 104(4/5):281-286 1982

Effects of cysteamine (Cys) on frequency of sister chromatid exchanges (SCE) in 5-bromo-2'-deoxyuridine (BUDR)-substituted cells exposed to UV or fluorescent light were studied in CHO cells. Data on av SCE/chromosome and the number of chromosomes analyzed in each treatment are presented. Results indicated that Cys does not produce any significant increase in SCE over the basal frequencies obtained with BUDR. However, UV and fluorescent light induced a 3-4-fold increase in the frequency of exchanges. Treatment with Cys during UV and fluorescent light irradiation produced a drastic reduction in SCE. (28 Refs)

157. EFFECT OF ACTIVATORS OF CAMP ACCUMULATION ON VARIOUS STAGES OF CELL GENOME EXPRESSION IN ACUTE RADIATION INJURY. COMMUNICATION 5. STUDY OF SEDIMENTATION CHARACTERISTICS OF RNP-PARTICLES RELEASED FROM THE CELL NUCLEI OF IRRADIATED AND PROTECTED WITH SEROTONIN ANIMALS

Tsadzerich BA, Galkina LA, Kucherenko NE
Faculty Biology, T. G. Shevchenko State Univ., Kiev, USSR
Radiobiologiia; 22(5):603-607 1982

Effect of the radioprotector serotonin (ST) on the release of ribonucleoprotein (RNP) particles from the cell nuclei was studied in male albino rats subjected to whole-body irradiation with 776 rad. S T (20 mg/kg, ip) was administered 15

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min prior to irradiation. Irradiation caused significant inhibition of RNP release from the nuclei of liver and of spleen cells. ST administration resulted in stabilization of RNP synthesis and release. It was concluded that the mechanism of the radioprotective effect of ST was associated with intracellular accumulation of cyclic AMP. (14 Refs)

158. EFFECT OF ACTIVATORS OF CAMP ACCUMULATION ON VARIOUS STAGES OF GENOME EXPRESSION DURING ACUTE RADIATION SICKNESS. 4. STUDY OF CYTOSOL FACTORS THAT CONTROL TRANSCRIPTION AND RNA RELEASE FROM THE NUCLEI AFTER IRRADIATION AND AFTER PREIRRADIATION TREATMENT WITH THE RADIOPROTECTOR SEROTONIN

Tsudzevich BA, Galkina LA, Kucherenko NE
Dept. Biochemistry, T. G. Shevchenko State Univ., Kiev, USSR
Radiobiologiia; 22(4):435-440 1982

Cytosol fractions from livers and spleen cells of normal rats, rats irradiated with 776 rads and rats subjected to preirradiation administration of the radioprotector serotonin (ST) were incubated with suspensions of isolated cell nuclei. Analysis of transcription and RNA release from the nuclei showed that the whole-body irradiation caused progressive inhibition of activity of cytosol protein factors. The administration of serotonin enhanced the rate of transcription and release of messenger RNA from the nuclei. (15 Refs)

159. EFFECT OF ACTIVATORS OF CAMP ACCUMULATION ON VARIOUS STAGES OF GENOME EXPRESSION DURING ACUTE RADIATION INJURY. COMMUNICATION 3. COMPARATIVE ANALYSIS OF PROPERTIES OF RNA SYNTHESIZED IN ISOLATED NUCLEI OF LIVER AND SPLEEN FROM IRRADIATED RATS PRETREATED WITH SEROTONIN

Tsudzevich BA, Galkina LA, Kucherenko NE
Biology Faculty, T. G. Shevchenko State Univ., Kiev, USSR
Radiobiologiia; 22(3):379-383 1982

The mechanism of radioprotective effect of serotonin was studied in cell nuclei isolated from the liver and spleen of irradiated rats subjected to whole-body irradiation with 800 rads. Fractionation of RNA synthesized in the isolated cell nuclei showed that irradiation inhibited the transcription, processing, and release of messenger RNA. Activation of cAMP system (pretreatment with serotonin) increased the radioresistance of RNA synthesis. (10 Refs)

160. EFFECT OF ACTIVATORS OF CAMP ACCUMULATION ON DIFFERENT STAGES OF GENOME EXPRESSION DURING ACUTE RADIATION INJURY. COMMUNICATION 2. EFFECT OF SEROTONIN AND PAPAVERINE ON TEMPLATE ACTIVITY OF NUCLEAR CHROMATIN FROM LIVERS AND SPLEENS OF RATS SUBJECTED TO WHOLE-BODY X-IRRADIATION

Tsudzevich BA, Galkina LA, Kucherenko NE
Faculty Biology, T. G. Shevchenko State Univ., Kiev, USSR
Radiobiologiia; 21(5):654-659 1981

Administration of serotonin (ST) and papaverine (PV) to rats prior to whole-body x-irradiation prevented the inhibition of template activity of spleen chromatin and stimulated the template activity of liver chromatin. It was suggested that the radioprotective effect of activators of cyclic AMP is associated with increased radioresistance of early stages of genome expression. (11 Refs)

161. STUDIES OF THE EFFECT OF SUPEROXIDE DISMUTASE ON THE RADIATION-INDUCED CHANGES IN DNA MOLECULE. III. STUDIES ON DNA STRAND BREAKS AND DEOXYRIBOSE DAMAGE UNDER AEROBIC AND ANAEROBIC CONDITIONS

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Stud Biophys; 82(3):229-234 1981

The radioprotective effect of superoxide dismutase (SOD) was studied in chicken RBC DNA irradiated with 60Co gamma rays under aerobic or anaerobic conditions. The radioprotective effect of SOD was greater in the presence of oxygen. It was concluded that the protective effect of SOD can be attributed to the fact that it acts like an enzyme. (7 Refs)

162. RADIOPROTECTIVE ACTIVITY AND SOME ASPECTS OF MECHANISM OF ACTION OF BIOGENIC AMINES IN MAMMALIAN CELLS CULTURED IN VITRO

Gracvskii EI, Ianusbevskaia MI, Buevcrova EI, Bragina EV, Konstantinova MM
N. K. Kol'tsov Inst. Biology of Development, Moscow, USSR
Radiobiologiia; 21(5):683-687 1981

The mechanism of radioprotective activity of the biogenic amines serotonin and adrenaline was studied in cultured Chinese hamster fibroblasts. Incubation of the fibroblasts with biogenic monoamines at 5 x 10(-3) M prior to irradiation with 300 R increased survival of the cells by approx 30%. A similar increase in survival was observed when the cells were incubated with serotonin after they were irradiated. Addition of serotonin prior to or after irradiation decreased the frequency of radiation-induced chromosome aberrations. Addition of adrenaline after irradiation failed to increase survival or to decrease the frequency of chromosome aberrations. (20 Refs)

163. CYTOGENETIC ANALYSIS OF MOUSE BONE MARROW RADIOPROTECTION WITH INTERFERON INDUCER POLY-I-POLY-C

Zbukova NA, Palyga GF, Maksimenko AA, Zavitaeva TA
Res. Inst. Medical Radiology, Obninsk, USSR
Stud Biophys; 86(3):205-210 1981

The radioprotective effect of interferon inducer poly I-C was studied in male (CBA x C57BL)F1 mice. Animals were subjected to whole-body gamma irradiation with 100, 200, and 400 rads; 48 hr prior to irradiation, animals were injected ip with poly I-C (0.2 ml). Prophylaxis administration of poly I-C reduced the incidence of chromosome aberrations in the bone marrow of irradiated mice. The most pronounced decrease of the frequency of chromosome and chromatid aberrations was observed after irradiation with 400 rads. (11 Refs)

164. INFLUENCE OF CYSTEAMINE AND RTG IRRADIATION ON MITOTIC ACTIVITY AND CHROMOSOMAL ABNORMALITIES IN REGENERATING LIVER OF RATS

Kropacova K, Misurova E, Praslicka M
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Radiobiol Radiother (Berl); 21(1):55-67 1980

The effect of cysteamine administration (10 mg/100 g, ip) 30 min before or after whole-body irradiation (600 R) on mitotic index (MI), metaphase to prophase ratio (M/P), and the frequency of chromosome abnormalities was studied in regenerating rat liver. When applied before irradiation, cysteamine exerted a significant protective effect against radiation-

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induced changes in MI and M/P; this effect was less apparent when cysteamine was applied after irradiation. The frequency of radiation-induced chromosome aberrations was suppressed by cysteamine, whether it was applied before or after irradiation. (33 Refs)

165. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY THIOL AND HYDRAZINE COMPOUNDS

MacRae WD, Stich HF
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Mutat Res; 68(4):351-365 1979

Sister chromatid exchanges (SCE) were sought in log phase cultures of chinese hamster ovary (CHO) cells exposed to cysteine (C), cystamine (CT), glutathione (G), 1,2-dimethyl hydrazine (DMH), isoniazid (INH), hydrazine dihydrochloride (HYD) or hydrogen peroxide (HP) either acutely (2-3 hr followed by wash out) or chronically (24 hr continuous exposure); the co-administration of copper (Cu, 10(-5) M) or manganese (Mn, 10(-5) M) and/or catalase (0.2 mg/ml) was also tested for effects on incidence of SCE. 5'-Bromodeoxyuridine (BrdU) (2 x 10(-5) M) was added after acute exposure or during chronic exposure and the cultures protected from light until harvest; 2 hr before harvest, colchicine (5 x 10(-5) M) was added to cause metaphase arrest and cultures subsequently examined for differential staining of sister chromatids of bromodeoxyuridine (Brd-U) substituted chromosomes using a modification of the technique of Korenberg and Freedlander. Uniformly stained cells were given a value of 0 (2 complete cell divisions); partially stained cells, a value of 1 (less than 2 divisions completed); cells with no mitotic activity were given a value of 2; and disrupted cells, a value of 3, on an arbitrary toxicity scale. Acute exposure to C, CT and G produced bimodal increases (3-4 x) in the prevalence of SCE at low (1.6 x 10(-4) M) and high (2 x 10(-2) M) concentrations with no effect at intermediate concentrations (2.5 x 10(-3) M). The presence of C, CT and G in chronic cultures increased SCE 4 x at a dose of 3.7 x 10(-4) M; higher doses were toxic. The presence of Cu increased toxicity generally and in a few instances, increased the number of SCE. DMH, INH and HYD produced a 2 x increase of SCE after chronic exposure at 10(-3) M; HP produced the same effect at a much lower concentration (3.9 x 10(-6) M); addition of Cu had no effect, but addition of Mn markedly increased toxicity and numbers of SCE. Catalase was able to reduce the incidence of SCE caused by DMH, INH and HP in the presence or absence of Mn; higher concentrations of DMH or INH could overcome the effect of catalase suggesting a dose response curve shift. Thiol and hydrazine containing compounds can induce genetic damage in vitro probably by a mechanism involving the formation of HP and free radicals. (50 Refs)

166. PROTECTION AFTER X-IRRADIATION BY 1,4-DITHIOTHREITOL OF TWO MAMMALIAN CELL TYPES IN VITRO

Bick YA, Brown JK
Dept. Zoology, Univ. Tasmania, PO Box 252c, Hobart, Tasmania 7001, Australia
Cytobios; 25(99/100):163-174 1979

DTT (1,4-dithiothreitol) was found to diminish the amount of chromosomal breakage in WBC cultures of the marsupial Potorous tridactylus and in the Don strain of Chinese hamster cells (LHI). The max decrease of damage in Potorous lymphocytes was to 54% of that of the irradiated cells without DTT treatment, and to 64% in the case of the Chinese hamster cells. For both cell types, it was shown that the most significant effect of DTT was due to its presence in the first 30 min postirradiation. The protective action of this sulfhydryl compound occurred even when DTT was not present during irradiation but was introduced as soon as possible after the X-ray dose was delivered. (Author abstract) (12 Refs)

167. EFFECT OF RADIOPROTECTORS FROM DIFFERENT CLASSES OF CHEMICAL COMPOUNDS ON DNA SYNTHESIS IN RADIOSENSITIVE TISSUES

Chigareva NG
No affiliation given
Radiobiologiia; 19(3):416-419 1979

The effects of radioprotectors on DNA synthesis are examined; sulfur-containing radioprotectors, (cystamine and S-aminopropyl-beta-aminoethylthiophosphate (APAETP) and radioprotectors from the group of benzothiadiazols including 4-amino- and 4-oxybenzo-2,1,3-thiadiazol (ABT and OBT), 4-oxy-5-aminobenzo-2,1,3-thiadiazol: (O-5-BT) and 4-oxy-7-aminobenzo-2,1,3-thiadiazol (O-7-BT)) were studied. Albino mice were inoculated ip with APAETP and cystamine at optimal protective doses (100 and 150 mg/kg, respectively), and with benzothiadiazols at max permissible doses (50 mg/kg for ABT, 40 mg/kg for OBT and O-5-BT, and 20 mg/kg for O-7-OT). Rats were sacrificed either 30 min or 3 hr after inoculation, and synthesis in the spleen and mucosa of the small intestine was determined; 40 min prior to sacrifice, the animals were inoculated ip with 3H-thymidine at 1 uCi/g. Preliminary experiments had shown that cystamine, APAETP, ABT and OBT allowed survival of 70-80% of mice irradiated with minimal lethal dose (no further details given); O-5-BT had mild radioprotective properties (35-40% survival), while O-7-BT had no radioprotective effect. It was found that effective radioprotectors caused transient inhibition of DNA synthesis in radiosensitive tissues; 30 min after administration of radioprotectors, incorporation of the label into spleen DNA decreased 20-40%. The degree of inhibition was not correlated with radioprotective activity. In contrast, only APAETP, cystamine, ABT and OBT caused inhibition (20-30%) of label incorporation into small intestine DNA; O-5-BT and O-7-BT did not change the rate of DNA synthesis. Three hr later, there was a normalization of DNA synthesis in both the spleen and small intestine after administration of the effective radioprotectors, but continued inhibition of DNA synthesis after O-7-BT administration (58% in the spleen and 41% in the small intestine). (14 Refs)

168. RADIOPROTECTION BY DMSO OF MAMMALIAN CELLS EXPOSED TO X-RAYS AND TO HEAVY CHARGED-PARTICLE BEAMS

Chapman JD, Doern SD, Reuvers AP, Gillespie CJ, Chatterjee A, Blakely EA, Smith KC, Tobias CA
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Radiat Environ Biophys; 16(1):29-41 1979

Results of studies designed to measure the radioprotective effectiveness of dimethylsulfoxide (DMSO) against x-rays and heavy charged-particle radiations were reported. Chinese hamster cells (V79) were synchronized by a procedure of mitotic selection from monolayers. Cells (90% G1-phase) were irradiated in stirred suspensions containing various concentrations of DMSO. Chemical radioprotection of cell inactivation was observed for all rate of energy loss (LET) values studied. When cell survival data were resolved into linear and quadratic components, the extent and concentration dependence of DMSO protection were found to be different for the single and double event mechanisms. When G1-phase cells were irradiated with x-rays, the concentrations of DMSO required to produce half-max protection were approx

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600 and 200 milliM for single- and double-events, respectively. X-irradiation of mitotic cells showed that the max extent of protection was 83 and 55% for single- and double-event mechanisms. The concentration of DMSO resulting in half-max protection of mitotic cells was approx 500 and 80 milliM for single- and double-events, respectively. The proportion of DMSO protection against the single-event mechanism was not significantly different for x-rays, helium-, carbon-, or neon-ions. The data confirm the reports that DMSO can radioprotect mammalian cells against inactivation by x-rays and indicate that it can radioprotect mammalian cells against the lethal action of heavy charged-particle irradiation. (24 Refs)

169. STUDIES OF THE EFFECT OF SUPEROXIDE DISMUTASE AND CHEMICAL RADIOPROTECTORS (CYSTEINE AND GLUTATHIONE) ON RADIATION-INDUCED CHANGES IN THE DNA MOLECULE. I. STUDIES OF TM AND BASE DESTRUCTION

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Stud Biophys; 71(1):9-13 1978

Radiation damage to calf thymus DNA irradiated with 86 kilorads/hr 60Co-gamma irradiation in the presence of superoxide dismutase (SOD) was assessed to evaluate the possible radioprotective effect of SOD compared with that of cysteine and glutathione. Radiation damage to DNA was estimated by determi nation of Tm (midpoint of melting-hybridization), temperature dependence of light absorbance, and changes in characteristic absorbance due to destruction of nitrogen bases. SOD was obtained from pig liver. Irradiated DNA preparations contained 1.33% protein, 7.4% phosphorous, 13.8% nitrogen, 92.24% DNA and 6.1% RNA. Tm amounted to 85.70 +-1.29 and 87.11 +-0.47 without radioprotector at 0 kilorads. These data concur with data relating the nucleotide composition of calf thymus DNA to Tm. SOD preparations had specific activities of 889 units/mg protein and 728 units/mg protein. Results clearly demonstrated that cysteine and glutathione prevented radiation-induced denaturation of DNA. The differences in Tm values for DNA irradiated with doses of 10-30 kilorads in the presence and absence of cysteine or glutathione were significant (p less than 0.01 or p less than 0.001). Approx full protection of nitrogenous bases in DNA irradiated with 50 and 100 kilorads by cysteine and glutathione was observed. A decrease in Tm was observed in native DNA when glutathione was added because of the destabilizing effect of this compound. A significant (p less than 0.05, p less than 0.01, or p less than 0.001) radioprotective effect of SOD on DNA was noted. Small differences between radioprotection by active versus denatured SOD were not significant. Estimates of base damage were inconclusive. (13 Refs)

170. COMPARATIVE STUDIES ON PROTECTIVE EFFECT OF VARIOUS SULFHYDRYL COMPOUNDS AGAINST CELL DEATH AND DNA STRAND BREAKS INDUCED BY X-RAYS IN CULTURED MOUSE L CELLS

Mori T, Horikawa M, Nikaido O, Sugahara T
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J Radiat Res (Tokyo); 19(4):319-335 1978

The protective effects of ten sulfhydryl (SH) compounds were investigated for their protective effect against cell death and DNA strand breaks induced by x-rays in cultured mouse L cells. The SH compounds were divided into three classes according to their radioprotective action and toxicity as measured by colony forming ability in irradiated and unirradiated mouse L cells. The protective effects of representative compounds from each class (cysteamine, 2-aminoethylisothiuronium bromide hydrobromide (AET) and 2-mercaptopropinonylglycine (MPG)) against the formation of single- and double-strand breaks in DNA induced by x-rays were determined. The DNA strand breaks were protected effectively by cysteamine and to a lesser extent by AET. Significant radioprotective effect was not observed with MPG. It is shown that x-ray induced single-strand breaks can be rejoined during postirradiation incubation in SH compound-free medium. Most of the double-strand breaks, however, were not repaired, even after prolonged postirradiation incubation. These results indicate that there may be a correlation between protection against cell death and protection against the formation of DNA double-strand brea ks, because the three SH compounds used were radioprotective against x-ray induced cell death and double-strand breaks in the order of 60 milliM (mM) cysteamine, 30 mM AET and 0.02 mM MPG. (31 Refs)

B.
Radioprotectors and Cyclic Nucleotide Related Effects

171. EFFECT OF WR-2721 ON CYCLIC AMP LEVELS IN RAT PAROTID GLAND (MEETING ABSTRACT)

Menard TW, Watson EL, Edmondson SW, Singh JC, Krohn KA
Univ. of Washington, Seattle, WA 98195
Thirty-third Annual Meeting of the Radiation Research Society May 5-9, 1985, Los Angeles, California, p. 42, 1985.

Elevation of endogenous intracellular levels of cAMP has been proposed as a mechanism for the radioprotective action of WR-2721 demonstrated for rat parotid salivary gland. To evaluate this mechanism radioimmunoassay was used to measure intracellular levels of cAMP in rat parotid gland 15 and 30 min following administration of WR-2721 (200 mg/kg, IP) in male Sprague Dawley rats. Control rats received diluent only (negative controls) or isoproterenol (5 mg/kg, IP), a compound known to elevate intracellular cAMP levels. While the isoproterenol treated animals demonstrated characteristic elevation of cAMP levels, there was no significant difference between WR-2721 treated animals and negative controls at either time point. Cyclic AMP values (picomoles/mg protein) at 15 min were: negative control (19.4 +/- 1.2); WR-2721 (22.1 +/- 2.3). Thirty min values were: negative control (26.3 +/- 4.1); WR-2721 (25.7 +/- 2.0). These findings indicate that elevation of endogenous cAMP levels is not the mechanism by which WR-2721 confers protection to parotid salivary gland in rats. The mechanism(s) of protection remains to be elucidated.

172. ADENOSINE-3',5'-CYCLIC MONOPHOSPHATE (CAMP) PROTECTS MOUSE NEUROBLASTOMA CELLS AGAINST RADIATION DAMAGE (MEETING ABSTRACT)

Deisch RM, Rama BN, Prasad KN
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Second International Conference on the Modulation and Mediation of Cancer by Vitamins and Micronutrients. Tuscon, Arizona, February 10-13, 1985, Arizona Cancer Center and International Association of Vitamin and Nutritional Oncology, abstract P-14, 1985.

Several previous studies, including our own, have shown that an elevation of cAMP protects normal cells against radiation damage. The purpose of this study was to investigate the role of prostaglandin (PG)A2, a stimulant of adenylate cyclase, and 4-(3-butoxy-4-methoxybenzyl)-2-imidazolidinone (Ro20-1724), an inhibitor of cAMP phosphodiesterase in modifying the radiation response of mouse neuroblastoma

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(NBP2) cells in culture. Cells were treated with PGA2 (5 ug/ml) or Ro20-1724 (100 ug/ml) either 15 min before and during irradiation or immediately after irradiation for 15 min. Radiation was delivered from a 60Co-gamma-radiation source at a dose rate of 24 rad/min. Cells were irradiated at roo m temperature; they were washed twice with the growth media immediately after drug treatment. The number of colonies per dish was determined 7 days after irradiation. Results showed that both PGA2 and Ro20-1724 increased the survival of NBP2 cells when given before and during irradiation (PGA2 increased survival from 57% to 83% at 200 rad); whereas, they were ineffective when given after irradiation. Both agents were more effective at lower radiation doses. Both PGA2 and Ro20-1724 are known to increase the intracellular level of cAMP in these cells by about 5-fold. Therefore, the radioprotective effect of PGA2 and Ro20-1724 is mediated by a cAMP-dependent mechanism.

173. CYCLIC NUCLEOTIDE LEVELS IN THE REGENERATING LIVER OF RATS FOLLOWING IRRADIATION AND PROTECTION BY SEROTONIN

Aslamova LI, Blium IaB, Tsudzevich BA, Kucherenko NE
Radiobiologiia; 25(3):324-7 1985

Changes in cAMP and cGMP levels after X-irradiation and radioprotective treatment with serotonin were studied using a model of impulse inhibition and repair of transcription, translation and replication by cycloheximide in rat hepatocytes in vivo. Irradiation was shown to inhibit the cyclic nucleotide synthesis. Serotonin increased the contents of cAMP and cGMP maintaining their elevated level after X-irradiation.

174. WORK IN PROGRESS: RADIOPROTECTION OF HUMAN BREAST CANCER CELLS BY ELEVATION OF INTRACELLULAR CYCLIC AMP

Griem K, Weichselbaum RR, Umans RS, Gifford L, Little JB
Laboratory of Radiobiology, Harvard School of Public Health, Boston, Massachusetts.
Radiology; 148(1):289-90 1983

MCF-7 human breast cancer cells that were treated for one hour prior to X irradiation with the cyclic AMP-inducing agent 1-methyl-3-isobutylxanthine displayed a slight but significant increase in surviving fraction over untreated controls at each radiation dose level. This was accompanied by a two-fold increase in the level of intracellular cyclic AMP.

175. EFFECTS OF WR 2721 ON CYCLIC NUCLEOTIDE LEVELS AND LYSOSOMAL ENZYME ACTIVITIES

Trocha PJ, Catravas GN
Biochemistry Dept., Armed Forces Radiobiology Res. Inst., Bethesda, MD, 20814
Int J Radiat Oncol Biol Phys; 8(3/4):543-546 1982

Effects of WR 2721 administered ip to Sprague-Dawley rats 30-40 min prior to exposure to 1,000 rad 60Co on cyclic nucleotide levels and lysosomal enzyme activities were studied. WR 2721 caused changes in cyclic nucleotide levels and beta-glucuronidase activities in spleen and liver and the changes were greater in the spleen than liver. It is suggested that WR 2721 imparts its radioprotective effect to mammalian systems by altering cell populations in radiosensitive tissues (spleen), resulting in modifications of cyclic nucleotide levels and lysosomal activities in irradiated and unirradiated animals. (7 Refs)

176. EFFECT OF PURINE NUCLEOSIDES AND NUCLEOTIDES ON THE IN VIVO RADIATION RESPONSE OF NORMAL TISSUE IN T HE RAT

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Int J Radiat Oncol Biol Phys; 7(3):365-369 1981

The effect of inorganic phosphate (IPP) on normal tissue tolerance and tumor control in irradiated WAG/Rij rats was investigated. At day 25, following 2250 rads, scores of 1.8 +-0.1 (breakdown of skin), 0.5 +-0 (no effect), and 0.3 +-0.3 (severe reddening and scaling) were observed for saline, IPP-0 (IPP treated immediately prior to irradiation), and IPP-4 (IPP treated 4 hr prior to irradiation) groups of rats, respectively. Differences between IPP-0 and saline groups and between IPP-0 and IPP-4 groups were statistically significant. IPP-0 groups showed greater protection against structural damage than did saline and IPP-4 groups following single doses of radiation. Protection was max when IPP was administered at closer intervals prior to irradiation. Animals injected with pyruvate or phosphate underwent radiation-induced skin changes that did not differ from those of saline-injected controls. Skin reactions were significantly reduced in rats treated with inosine alone. Radioprotection also was observed with the purine nucleosides, adenosine and guanosine, and the purine nucleotides, cyclic AMP, AMP, 5'-inosine monophosphate, and 5'-guanosine monophosphate. The purine bases, hypoxanthine, adenine, and guanine were not protective. A decrease in blood pressure was observed following the administration of either IPP or inosine alone but not following AMP or cyclic AMP. The mechanism of radioprotection is discussed. (20 Refs)

177. MECHANISM OF RADIOPROTECTIVE EFFECT OF BETA-MERCAPTOETHYLAMINE MEDIATED VIA THE SYSTEM OF CYCLIC NUCLEOTIDES

Nikolskii AV, Aripov ShM, Pushkareva NB, Romantsev EF
No affiliation given
Radiobiologiia; 21(3):363-367 1981

To evaluate the mechanism of radioprotective activity of mercaptoethylamine (MEA), (CBAxC57Bl)F1 mice received single ip injection of MEA (150 mg/kg). Within different time periods after administration, animals were sacrificed and the ratio of cyclic AMP (cAMP) and cyclic GMP (cGMP) in the liver was determined. Significant increase of cAMP:cGMP ratio and cAMP content was recorded only within 15 min after MEA administration. (21 Refs)

178. MODIFICATION OF RADIOSENSITIVITY OF MAMMALIAN CELLS BY CYCLIC NUCLEOTIDES

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Life Sci; 29(1):1-4 1981

Some in vitro and in vivo studies suggest that adenosine 3',5'-cyclic monophosphate (cyclic AMP) may be one of the important factors in determining the radiosensitivity of certain mammalian cells; however, the role of guanosine 3',5'-cyclic monophosphate (cyclic GMP) in radiosensitivity of mammalian cells is completely unknown. Recent data also suggest that the mechanism of radiation protection afforded by moderate hypoxia and SH-containing compounds may involve an alteration in the intracellular level of cyclic AMP. At least one in vivo study shows that cyclic AMP protects hair follicles and gut epithelial cells against radiation damage; however, it does not protect lymphosarcoma and breast carcinoma in mice. If a similar phenomenon is found in humans, an elevation of the intracellular level of cyclic

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AMP during radiation exposure may improve the effectiveness of radiation therapy in those cases where the radiation damage of normal tissue becomes the limiting factor for a continuation of the therapy program. More in vitro and in vivo studies on normal and cancer cells are needed to substantiate the role of cyclic nucleotides in radiosensitivity. (Author abstract) (15 Refs)

179. RADIOPROTECTION OF MOUSE INTESTINE BY INHIBITORS OF CYCLIC AMP PHOSPHODIESTERASE

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Int J Radiat Oncol Biol Phys; 5(6):825-833 1979

The radioprotection of mouse intestine by inhibitors of cyclic (c)AMP phosphodiesterase, including methyl xanthines, caffeine, 1-methyl-3-isobutyl xanthine (MIX), diethyl-amino-1-reserpine (DL-152) and 4(3-butoxy-4-methoxylbenzyl)-2 (RO-20-1724), was investigated. The capacity of these inhibitors was assayed by the survival of colony-forming units of the jejunal crypt. The capacity of these compounds to protect crypt stem cells against killing by x-rays was critically dependent upon timing and mode of administration. Optimum survival of crypt stem cells was found after ip administration of DL-152 60-120 min prior to irradiation or MIX given 30 min before irradiation, and after iv administration of caffeine 60-120 min before irradiation or theophylline given 60 min before irradiation. Crypt-cell survival could be enhanced by a factor of 6-7 when these protocols were used. Some elevation of cAMP content of the whole jejunum was induced by all the compounds, simultaneous with or preceding the period of max radioprotection. Cyclic AMP was localized with immunofluorescent staining. After DL-152 injection, cAMP was elevated in all regions of the jejunum, but to the greatest extent in the lower part of the crypt. That the mechanism of protection does not depend upon the induction of hypoxia is suggested by the finding of similar survival curves in crypt stem cells from MIX and DL-152 treated mice and the saline-injected controls. (27 Refs)

C.
Other Subcellular Effects of Radioprotectors

180. PROTECTION OF NORMAL AND GSH DEPLETED CELLS BY GLUTATHIONE ESTERS AND CYSTEAMINE (MEETING ABSTRACT)

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Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 2-7, 1985.

In 1983 Puri and Meister (PNAS 80, 5258) reported that administration of monomethylester and monoeth ylester of glutathione (GSH) leads to a substantial increase in the level of GSH in liver and kidney. Wellner et al (PNAS 81, 4732, 1984) observed that GSH ester caused a rise of the cellular GSH level in and afforded a radioprotection of human lymphoid cells and fibroblasts. However, Russo and Mitchell (Int J Rad Onc Biol Phys 10, 1243, 1984) observed no radioprotection of Chinese hamster cells after elevation of cellular GSH levels induced by other means. We studied radioprotection of HeLa cells by monomethyl and monoethyl GSH esters. HeLa cells as well as HeLa cells with depleted GSH levels due to BSO or DEM treatment were used. Clonogenicity was used as criterion for radiation damage. Cells were incubated under air in culture medium containing 16 or 64 mM GSH ester for 1-4 hr and some protection (DRF 1.1 and 1.3, respectively) was observed. The increase of cellular GSH after incubation with 1 mM methylester was 30-40%. GSH depletion with BSO caused a sensitization of anoxically irradiated cells with a factor of 1.4. Incubation of these cells with 16 mM GSH ester protected with a factor of 1.2-1.3. Thus radiosensitivity was restored to almost the level of cells not depleted for GSH. The intracellular GSH level rose from less than 5% to about 35% of non-depleted cells. Incubation with GSH itself had practically no effect on radiosensitivity or cellular GSH level. When non-depleted HeLa cells were protected with 16 mM cysteamine in anoxic condition radioprotection with a DRF of 1.8 was observed relative to non-protected cells in anoxic condition. GSH depleted cells in anoxic condition were also protected by cysteamine. The radiosensitivity of these cells was similar to cysteamine protected and non-GSH-depleted cells, thus cysteamine completely restored the radioresistance to the level of non-depleted and protected cells. Cysteamine did not cause an increase of the cellular GSH level. It is concluded that for radioprotection of cysteamine no rise of the cellular GSH level is required. (3 Refs)

181. SELECTIVE PROTECTION OF CELLS AGAINST X-IRRADIATION. ISOPROTERENOL PROTECTS ONLY THOSE CELLS THAT POSSESS BETA-ADRENORECEPTORS

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Experientia; 41(11):1430-2 1985

In mixed culture of Chinese hamster fibroblasts, clone 431, and transformed murine L fibroblasts, clone B-82, isoproterenol was found to protect only 431 cells against ionizing radiation. It was shown that 431 cells, in contrast to B-82 cells, possess beta-adrenoreceptors, and the radioprotective effect of isoproterenol can be realized only if this agent interacts with beta-adrenoreceptors coupled with the cAMP system. Since malignization often causes the disappearance of beta-adrenergic and other hormone receptors, the combined culturing and irradiation of the cells studied can be regarded as a model of the growth of malignant cells (B-82) among normal tissue cells (431 cells) under conditions of radiation therapy. A possibility of selective protection against radiation damage of normal tissue cells, with retention of the former radiosensitivity of tumor cells, is discussed.

182. IRON-CATALYZED GENERATION OF PENTANE FROM IRRADIATED ERYTHROCYTE MEMBRANES (MEETING ABSTRACT)

Kumar KS, Vaishnav YN, Sancho AM, Weiss JF
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Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 132, 1985.

We reported earlier that lipid peroxidation and pentane evolution occur in rat liver microsomes irradiated in vitro. Data presented here show that pentane is generated from human erythrocyte membranes upon irradiation (800 Gy, cobalt-60) as measured by gas chromatography. Malondialdehyde production, measured by the thiobarbituric acid assay, accompanied pentane evolution. Pentane evolution can be modified by the addition of iron and various protective agents. Irradiation in the presence of 0.1 mM Fe2+ (ferrous ammonium sulfate) increased pentane formation from 9 to 34 pmol/mg membrane protein. Addition before irradiation of hydroxyl radical scavengers, such as benzoate (5 mM), decreased pentane production from 34 to 14 pmol. Addition of WR-2721 resulted in a decrease in pentane to 15 pmol. Pentane production was greatly diminished by the presence of catalase or superoxide dismutase during irradiation. These studies suggest that oxygen radical species that are induced by ionizing

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radiation can affect mammalian cell membranes and this effect can be enhanced by iron, probably through catalysis of a Haber-Weiss type reaction. It is possible that Fe2+, which is oxidized to Fe3+ in this reaction, is regenerated by superoxide produced during irradiation.

183. EFFECT OF RADIOPROTECTIVE DRUGS ON GLUTATHIONE PEROXIDASE ACTIVITY (MEETING ABSTRACT)

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Thirty-Second Annual Meeting of the Radiation Research Society, March 25-29, 1984, Orlando, Florida, p. 97, 1984.

Previous studies from our laboratory have indicated that the activities of endogenous protective enzymes, eg, glutathione peroxidase and superoxide dismutase, are altered in some mouse tissues after irradiation. It is important also to determine the effect of radioprotective and sensitizing drugs on the activity of these enzymes to understand the role of endogenous protective systems in chemical modification of radiosensitivity. In the present study, various radioprotectants and sensitizers were added to mouse liver cytosol fraction, and glutathione peroxidase activity was determined using hydrogen peroxide or cumene hydroperoxide as substrate. In the absence of exogenous glutathione, WR-272 1, S-2-(3-aminopropylamino)-ethyl phosphorothioic acid, or its thiol WR-1065 did not substitute for glutathione as substrate for the enzyme. Coincubated with glutathione, WR-1065 inhibited glutathione peroxidase activity; the inhibition was much greater with cumene hydroperoxide as the substrate (66-78% with cumene hydroperoxide and 14-34% with hydrogen peroxide as substrate), as compared to the activity with glutathione alone. When mice were injected with WR-2721 (400 mg/kg, ip), serum glutathione peroxidase activity using either substrate was increased one hr after treatment. The effects of various drugs on tissue enzyme levels and on in vitro activity of the enzyme will be compared.

184. THE EFFECT OF GAMMA IRRADIATION AND CYSTAMINE ON SUPEROXIDE DISMUTASE ACTIVITY IN THE BONE MARROW AND ERYTHROCYTES OF RATS

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Radiat Res; 91(3):507-515 1982

The effects of gamma-irradiation and cystamine on the activity of superoxide dismutase (SOD) in the bone marrow and RBC were studied in male Wistar rats. Four groups of rats were used. Group 1 underwent irradiation only. Group 2 underwent cystamine treatment followed by irradiation. Group 3 underwent cystamine treatment only. Group 4 consisted of controls that did not undergo cystamine treatment or irradiation. Irradiation consisted of whole-body exposure to 8 Gray units. Cystamine treatment consisted of a single ip injection of 50 mg cystamine dihydrochloride administered 10 min before irradiation. Group 1 showed a decrease in SOD activity in the bone marrow lasting greater than 14 days after irradiation; SOD in the RBC was increased. The reduction in marrow SOD was less pronounced in Group 2 than in Group 1. SOD in the RBC was significantly greater in Group 2 than in Group 1. Group 3 showed decreased SOD in the marrow on day 3 only, and increased SOD in RBC, primarily on day 14. Group 1 showed a reduction in the cellularity of the bone marrow. In Group 2 this reduction was less pronounced. Cellular concentrations of SOD in the bone marrow were increased on day 3 in Group 2 and to a greater extent in Group 3. (33 Refs)

185. TRANSPORT AND RADIOPROTECTIVE ACTIVITY OF METHYLATED HEMATOPORPHYRIN IN CELL CULTURES

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No affiliation given
Radiobiologiia; 22(4):462-465 1982

The mechanism of the radioprotective activity of the methylated hematoporphyrin 2,4(alpha-methoxyethyl) deuteroporphyrin dipotassium salt (porphyrin MDP-IX) was studied in cultured SOC cells. The porphyrin MDP-IX was added to the culture media within different time periods before or after irradiation with 600 R. The modifying effect of the porphyrin MDP-IX was estimated on the basis of increase in cell survival. Addition of the porphyrin MDP-IX 8 hr prior to irradiation provided the max radioprotective effect. (13 Refs)

186. THE STABILIZING EFFECT OF ANTIOXIDANTS ON MEMBRANES EXPOSED TO RADIATION

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Radiobiologiia; 20(6):902-905 1980

Experiments were conducted to study a stabilizing effect of antioxidants (ubiquinone-coenzyme Q9, vitamin K1, 4-methyl-2,6-di-tertiary-butylphenol, 2-phenylbenzimidazole, phenylboren and 2,2'-dioxy-3,5,6,3',5',6'-hexachlorodiphenylsulfoxide) on mitochondrial membranes (from male Wistar rats) exposed to gamma-irradiation (800 rads). It was found that ubiquinone-coenzyme Q9 and other antioxidants caused a partial stabilization of mitochondrial membranes. A possible mechanism behind the radioprotective effect of the antioxidants is discussed. (16 Refs)

D.

The Role of Factors Influencing Effectiveness of Radioprotectors

1.

Tissue Oxygen Levels

187. PROTECTIVE EFFECTS OF 2-[(AMINOPROPYL)AMINO] ETHANETHIOL, EVEN UNDER CONDITIONS OF ACUTE HYPOXIA, AGAINST RADIATION-INDUCED MUTAGENICITY IN V-79 CELLS (MEETING ABSTRACT)

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Proc Annu Meet Am Assoc Cancer Res; 27:150 1986

We examined the effects of the radioprotector 2-[(aminopropyl)amino] ethanethiol (WR1065) on radiation-induced cell killing and mutagenesis at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus in V79 Chinese hamster cells under hypoxic or oxic conditions. Conditions of acute hypoxia were attained by gassing 10(6) cells in 1-ml vol in individual glass ampules for 2 min with nitrogen. Ampules were then sealed and incubated at 37 C for 60 min. Following this treatment, cell survival after irradiation was enhanced by a factor of 3. The effect of acute hypoxia on the formation of HGPRT mutants by irradiation was also investigated. Mutation frequencies were determined with a 6-day expression time and corrected for the number of spontaneous background mutants. Although mutation induction was linear as a function of radiation dose under most conditions tested, it was significantly reduced in hypoxic cell populations [eg, a mutation protector factor (MPF) of 3.2, as determined from a ratio of the slopes of the induction curves]. If cells were irradiated in air and then made hypoxic, no signif-

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icant reduction in mutation frequency was observed. In contrast, if WR1065 (4 mM) was added to cells made hypoxic immediately following irradiation in air, an MPF of 2.2 was observed. These results suggest that the anti-mutagenic effect of WR1065 is not due solely to its ability to scavenge radiation-induced oxygen free radicals, but rather that it may also modulate this effect thr ough either the scavenging of metabolically induced free radicals and/or the chemical repair of radiation-induced DNA lesions.

188. TUMOR RADIOSENSITIZATION WITH CONCOMITANT BONE MARROW RADIOPROTECTION: A STUDY IN MICE USING DIETHYLDITHIOCARBAMATE (DDC) UNDER OXYGENATED AND HYPOXIC CONDITIONS

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Int J Radiat Oncol Biol Phys; 11(6):1163-9 1985

We have established, both in vitro and in vivo, that Diethyldithiocarbamate (DDC) protects mammalian cells from radiation. The in vivo protection, when non-toxic concentrations of DDC are present one-half hour before irradiation, is reflected by a dose modification factor (DMF) of 1.9 based on LD50/30 and 1.5 using survival of CFUs as an endpoint. Further experiments in vivo have extended our knowledge to the differential radioprotective effects of DDC on the bone marrow of animals breathing room air compared to a 5.5% oxygen in nitrogen mixture. The DMF (LD50/30) for DDC in air breathing animals, previously established as 1.9, can be contrasted with a DMF, obtained in the present study, of 1.2 for animals irradiated in the hypoxic state. Moreover the DMF (CFUs survival) previously established at 1.5 for air breathing animals, can be compared to a value of 1.3, obtained in the present study, for mice irradiated under hypoxic conditions. Modification of the dose response by DDC, for both bone marrow and tumor, was also examined in animals bearing a RIF sarcoma. Although protection of the bone marrow was confirmed (DMF = 2.1), the striking finding was that the tumor cells were sensitized, in both air breathing and nitrogen breathing animals, by the addition of DDC one-half hour before the radiation exposure. Moreover, the tumor radiosensitization, a factor greater than 2, in air breathing animals, appeared to be independent of dose (D0 = 200 rad, with or without DDC). The tumor radiosensitization was even more marked in the nitrogen breathing mice, in which a factor of 10 difference in survival was noted, together with a tendency towards greater sensitization at radiation doses in the clinical range. The results, demonstrating bone marrow radioprotection by DDC (aerobic greater than hypoxic) with concomitant tumor radiosensitization (hypoxic greater than aerobic) strongly suggest a large therapeutic gain factor (TGF) which could be further explored in a clinical setting.

189. INTERACTIONS OF RADIOPROTECTORS AND OXYGEN IN CULTURED MAMMALIAN CELLS. I. DITHIOTHREITOL EFFECTS ON RADIATION-INDUCED CELL KILLING

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Radiat Res; 101(3):424-33 1985

Radioprotection in vitro by sulfhydryl (SH)-containing compounds is usually greater in aerated than in hypoxic cells. This observation has been cited recently as one of the reasons for the relatively greater effectiveness of radioprotectors such as WR-2721 in normal tissues compared to tumor cells. It is demonstrated herein, however, that hypoxic V79 cells irradiated in vitro under carefully controlled conditions are protected to a greater extent by low concentrations (1-2 mM) of the SH compound dithiothreitol (DTT) than are aerated cells. The reverse, more general phenomenon is seen at high concentrations of DTT (greater than 2 mM). This complex SH concentration and oxygenation dependence results in an increase in the oxygen enhancement ratio (OER) at low concentrations of DTT relative to the OER in the absence of DDT, followed by a decrease in OER at concentrations greater than 2 mM DTT. The possible radiation chemical basis for this finding and its importance to the clinical use of SH-containing radioprotectors are discussed.

190. EFFECTS OF OXYGEN AND DTT ON DNA DAMAGE (MEETING ABSTRACT)

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Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 131, 1985.

The effects of oxygen and the sulfhydryl-containing radioprotector dithiothreitol (DTT) on DNA damage in irradiated Chinese hamster V79 cells have been investigated using the alkaline filter elution method. In the absence of radioprotector, the hypoxic DNA damage dose response curve depended on the length of time V79 cells were in exponential phase growth between subculturing and irradiation. Dose response curves for DNA from cells irradiated in air were identical regardless of whether the cells had been subcultured 24 or 48 hr prior to irradiation, but cells irradiated in hypoxia 24 hr after trypsinization and subculture displayed a dose response curve for DNA damage which was two times steeper than that obtained for cells irradiated in hypoxia 48 hr after subculture. When DTT was added to the cells during irradiation, the degree of radioprotection was dependent on the DTT concentration, the presence or absence of oxygen, and the time interval between subculture and irradiation. At high DTT concentrations radioprotection in air was significant and was independent of subculture time; in hypoxia the degree of protection was much greater in cells which were subcultured 24 hr prior to irradiation than in 48 hr cultures. Possible mechanisms for these effects were discussed.

191. THE ROLE OF GLUTATHIONE IN THE AEROBIC RADIORESPONSE:III. THE EFFECT ON RECOVERY BY DIFFERENT THIOL COMPOUNDS USED AT EQUIMOLAR THIOL CONCENTRATIONS (MEETING ABSTRACT)

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Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 2-9, 1985.

In the second stage of our study (The Role of GSH in the Aerobic Radioresponse: II - presented at th is meeting), we concluded that the recovery to the control aerobic radioresponse by extracellular GSH after intracellular GSH depletion may be enzymically mediated. In this - the third part of our study - we examined the uniqueness of GSH in affecting recovery by comparing its effect with those of other thiol compounds (used at equimolar thiol concentrations). Briefly, the experimental procedure consisted of exposing mammalian cells (attached in flasks and growing exponentially) to 1.0 mM BSO for 24 hr prior to irradiation with 50 kVp x-rays. Prior to irradiation, the medium was aspirated and replaced with a chemically defined salt solution +/- thiol. The concentrations of nonprotein thiols were determined using Ellman's reagent. Our experimental results showed that although exogenously added 5mM GSH/30 min prevented the

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increased aerobic radiosensitization, GSH was not unique in this function. Both dithiothreitol (DTT) and WR1065 added at 2.5 and 5 mM respectively for 30 min also were effective. However, another well-known thiol containing compound, N-acetylcysteine, did not significantly reduce the increased aerobic radiosensitization when used at 5 mM for 30 min. Moreover, the compound that failed to eliminate the increased sensitizing effect was found in high intracellular concentrations as determined using Ellman's reagent. We conclude from this study that the recovery to the control aerobic radioresponse does not depend specifically on GSH. Furthermore, the presence of a high intracellular concentration of thiols is not in itself sufficient for the maintenance of the control aerobic radioresponse.

192. HYPOXIC RADIOPROTECTION BY PERFUSION WITH DEOXYGENATED DEXTRAN-HEMOGLOBIN (MEETING ABSTRACT)

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Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 4-8, 1985.

Although radioprotection of normal tissues by hypoxia would allow the administration of increased doses of radiation for a more effective killing of anoxic tumor cells, the induction of hypoxia is not readily attained. Hypoxia brought about by cessation of blood flow due to a tourniquet is slow in onset, and may not be uniform in extent throughout a vascular bed. Accordingly we have investigated the perfusion of sequestering agent for oxygen as a possible means for achieving hypoxia. In this regard, dextran-hemoglobin offers important advantages. It is not immunogenic or associated with any known toxicity, has a high affinity for oxygen, and is capable of supporting life upon a complete substitution of erythrocytes. Perfusion of pig skin with deoxygenated dextran-hemoglobin gives rise to a radioprotection factor of 2.0 against necrotic damage despite the known propensity of normal skin tissue to hypoxia. Its effects on the radiosensitivity of murine normal and KHT-sarcoma tissues are e xamined. The disadvantage of this modality of hypoxic radiotherapy arises from the need for simultaneous perfusion and irradiation. The advantage is that it promises to be highly predictable in its physical effects, and widely applicable wherever regional perfusion is permitted. (4 Refs)

193. RADIOPROTECTION OF V79 CELLS BY GLUTATHIONE MONO ETHYL ESTER (MEETING ABSTRACT)

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Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 2-6, 1985.

One of the proposed functions of glutathione (GSH) is protection of cells against free radicals and reactive oxygen species formed in normal metabolism, metabolism of drugs, and as a result of ionizing radiation. A new method for increasing cellular GSH levels consists of administration of glutathione mono ethyl ester (L-gamma-glutamyl-L-cysteinyl-glycyl ethyl ester (GEE)). Chinese hamster V79 cells in monolayer were used and the dose reduction factor (DRF) was determined for GSH and GEE under hypoxic and aerated conditions after irradiation with 300 kVp x-rays at a dose rate of 4.6 Gy/min. Cellular GSH levels of 2 to 4 times control levels were found with GEE (10 mM), but no increase was found when cells were exposed to GSH (10 mM) for periods up to 6 hr. Under aerated conditions, GSH and GEE showed equivalent DRF values (1.25) despite the fact that the intracellular GSH levels in GEE treated cells were twice those of cells treated with GSH. Under hypoxic conditions the DRF's for GEE and GSH were similar although in this case the DRF was dose-dependent with a maximal protection factor of 1.3. No radioprotection was observed with GEE- or GSH-treated cells, when the drug was removed by washing the dishes prior to irradiation under aerated or hypoxic conditions. Equivalent radioprotection was found with cells that had normal levels of GSH and those that had GSH levels that were 2-4 times higher. Radioprotection was reversed when the drug was removed prior to irradiation even though the intracellular GSH levels were not affected. The radioprotection observed seems to be primarily extracellular.

194. INFLUENCE OF PH AND TEMPERATURE ON THE RADIOPROTECTIVE EFFECT OF CYSTEAMINE: IMPLICATIONS FOR MECHANISMS OF ACTION OF AMINOTHIOLS (MEETING ABSTRACT)

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Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-2, 1985.

It has been suggested that radioprotection by the aminothiol cysteamine, is not the result of reduction of free radicals or scavenging of hydroxyl radicals but due to the production of hypoxia because of spontaneous oxidation as well as cellular-linked enzyme catalyzed oxidations. The spontaneous an d the enzyme-linked oxidations are influenced by pH (hydrogen ion) and temperature. In light of previous considerations we have investigated the role of pH and temperature in radioprotection produced by cysteamine. Our results show that at pH 6.5 there is less radioprotection by cysteamine than at pH 7.4, and at pH 7.8. The dose reduction factors (DRF) are 1.5, 1.8 and 2.1 at pH 6.5, 7.4 and 7.8 respectively. There was no effect of pH (treatment) on control culture survival. We have also found that lowering the temperature decreased the DRF from 1.8 at 37 C to 1.25 at 0 C. There was no effect of temperature variation on the control cultures. Our results indicate that pH and temperature will influence the degree of protection afforded by cysteamine and suggest that resultant hypoxia produced by the previous mentioned reactions plays a major role in the radioprotecting mechanism. It is also possible that radioprotection by aminothiols in vivo may be different in tumors (low pH) than in normal tissue (high pH).

195. EFFECTS OF OXYGEN AND DITHIOTHREITOL ON RADIATION INDUCED DNA DAMAGE IN CELLS (MEETING ABSTRACT)

Held KD, Bren GD
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International Conference on Mechanisms of DNA Damage and Repair. Implications for Carcinogenesis and Risk Assessment. Invited and Short Oral Presentations. June 2-7, 1985, Gaithersburg, Maryland, 1985.

The effects of oxygen and the sulfhydryl-containing radioprotector dithiothreitol (DTT) on radiation-induced damage in DNA of Chinese hamster V79 cells have been investigated using the alkaline filter elution method. Radiation dose response curves for DNA from exponential phase cells irradiated in hypoxia 24 hr after subculturing are two times steeper than curves obtained for exponential cells irradiated in hypoxia 48 hr after subculturing, although dose response curves for DNA from cells irradiated in air are identical regardless of whether the cells were subcultured 24 or 48 hr prior to irradiation. When DTT is added to the cells during irradiation, the DNA is protected in a DTT-concentration dependent manner, but the degree of protection depends on the presence or absence of oxygen and the time after subculture

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at which radiation exposure occurs. At high DTT concentrations radioprotection in air is significant and is independent of the time interval between subculture and irradiation (eg at 50 mM the dose modifying factor, DMF, is about 3 for both 24 and 48 hr cultures). In hypoxia the degree of radioprotection is also large, but there is more protection of 24 hr cultures then of 48 hr ones (eg at 50 nM DTT DMF is about 5 for 24 hr cultures and about 3 for 48 hr cultures). These differential effects with subculture time are not found when damage to these same cells is assessed using either a cell survival assay or the DNA unwinding hydroxyapatite chromatography assay. Poss ible mechanisms for these differential effects of oxygen and DTT on DNA damage with subculture time were discussed.

196. THE OXYGEN DEPENDENCE OF PROTECTION BY AMINOTHIOLS: IMPLICATIONS FOR NORMAL TISSUES AND SOLID TUMORS

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Department of Experimental Radiotherapy, University of Texas M.D. Anderson Hospital and Tumor Institute at Houston.
Int J Radiat Oncol Biol Phys; 10(9):1495-501 1984

This paper reviews the role of oxygen in the protection of both normal tissues and tumors in vivo by WR-2721. Although the presence of hypoxic cells in tumors is well accepted, data are presented that suggest there is a range of oxygen concentrations and thus OERs in normal tissues in vivo, too, and that some may, in fact, be radiobiologically hypoxic. Thus, the range of protection factors in normal tissues (which appears unrelated to tissue drug levels), as well as tumors can perhaps be explained by the range of OERs in these same tissues. The question of whether protection decreases with radiation dose per fraction is related to the distribution of oxygen in both normal tissues and tumors, i.e., whether oxygen is homogeneously or heterogeneously distributed among the cells. It is hypothesized that sulphydryl compounds may equalize the OER differential between tumors and normal tissues and thus remove the natural advantage (radioresistance) of the tumor when treated with radiation. Thus, no loss of therapeutic benefit would occur when sulphydryl compounds were given with radiation if the normal tissue were better oxygenated than the tumor. (50 Refs)

197. ENHANCEMENT OF CYSTEAMINE CYTOTOXICITY BY HYPERTHERMIA AND ITS MODIFICATION BY CATALASE AND SUPEROXIDE DISMUTASE IN CHINESE HAMSTER OVARY CELLS

Issels RD, Biaglow JE, Epstein L, Gerweck LE
Edwin L. Steele Laboratory of Radiation Biology, Department of Radiation Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.
Cancer Res; 44(9):3911-5 1984

Chinese hamster ovary cells were exposed to the sulfhydryl compound cysteamine at concentrations ranging from 0 to 8 mM for 120 min. No toxicity was found in cells maintained at 5 degrees during treatment; however, at 37 degrees and 44 degrees a paradoxical toxicity was observed, i.e., substantial toxicity was observed at cysteamine concentrations of 0.2 to 1 mM but decreased at higher drug concentrations. When drug-treated cells were exposed to a 30-min 44 degrees -heat treatment (surviving fraction, 0.15 in the absence of drug) toxicity was markedly enhanced. At 0.4 mM cysteamine, the surviving fraction was approximately 0.6 at 5 degrees, 0.01 at 37 degrees, and 0.00008 when the 44 degrees -heat treatment was also used. Cysteamine toxicity was not modified by the addition of superoxide dismutase (10 micrograms/ml) but was completely blocked by the addition of catalase (50 micrograms/ml) over the drug concentration range of 0.2 to 2.0 mM. Cysteamine autoxidation as measured by O2 upta ke at 0.4 mM proceeds through hydrogen peroxide (H2O2) production as evidenced by the regeneration of O2 upon the addition of catalase. In contrast, at 4.0 mM cysteamine, O2 regeneration was not pronounced. The data suggest that the production of H2O2 is the first reaction step in the mechanism of cysteamine toxicity. The subsequent production of highly reactive oxygen species like hydroxyl radicals (.OH) from H2O2 in the presence of reduced metal (Fenton chemistry) probably leads to the observed cellular toxicity.

198. THE INFLUENCE OF X RAY DOSE LEVELS ON NORMAL TISSUE RADIOPROTECTION BY WR-2721

Rojas A, Denekamp J
Gray Laboratory, Cancer Research Campaign, Mount Vernon Hospital, Northwood, Middlesex, UK.
Int J Radiat Oncol Biol Phys; 10(12):2351-6 1984

A variation in the degree of radioprotection by WR-2721 with X ray dose level is detectable in several normal tissue studies. A similar effect in tumors has been attributed to differential protection of oxic and hypoxic cells. For normal tissues it was previously postulated that it resulted from greater protection of 1 hit damage at low doses, with less protection of multihit damage. However, more extensive analysis of the normal tissue data, including both single dose and fractionated results show that it is not a universal effect in all normal tissues. It now seems more likely that varying PF values result from differential protection of cells at different oxygen tensions, even though the heterogeneity of oxygenation may not be detectable in the response to X rays alone.

199. LUNG RADIOPROTECTION BY WR-2721 AT LOW X-RAY DOSES PER FRACTION

Parkins C, Fowler JF, Denekamp J
Gray Laboratory of the Cancer Research Campaign, Mount Vernon Hospital, Northwood, Middlesex, U.K.
Eur J Cancer Clin Oncol; 20(11):1445-50 1984

The response of mouse lungs to single doses and ten fractionated irradiations has been tested using breathing rate and lethality as assays for damage. The radioprotective effect of 300 mg/kg WR-2721 has been determined for mice breathing air or 10% oxygen. The protection factor was assessed from dose response curves obtained at monthly intervals from 24 to 48 weeks. A low protection factor (1.2-1.4) was observed for single doses in air or 10% oxygen and also for ten fractions in air. Considerably more protection was seen with ten fractions in mice breathing the reduced oxygen concentration (protection factors of PF = 1.5-1.7). It is postulated that the low PF values normally reported for lung are due to the naturally high oxygen concentration in all cells in this tissue. A fraction of the cells becomes sufficiently hypoxic in 10% oxygen to be susceptible to WR-2721 radioprotection. This subpopulation can then be detected with small X-ray fractions (less than or equal to 5 Gy) but not with large single doses.

200. RADIOPROTECTION BY WR-2721 IN VITRO AT LOW OXYGEN TENSIONS: IMPLICATIONS FOR ITS MECHANISMS OF ACTIO N

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Br J Cancer; 47(3):387-392 1983

Radioprotection of spheroids of Chinese hamster V79 cells by WR-2721 was found to be a function of spheroid size, with the greatest dose-modifying effect by the protector observed for spheroids almost large enough to contain radioresistant 'anoxic' cells. The nature of the response suggested

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that most of the protective effect was due to the presence of an increased hypoxic fraction in the drug-treated spheroids. Similarly, when single-cell suspensions were irradiated at various oxygen tensions, one component of radioprotection by WR-2721 was found to be highly dependent upon the available oxygen. Two mechanisms of radioprotection of V79 cells by WR-2721 were thus demonstrated: a modest, oxygen-independent effect, presumably due to hydrogen donation, and an oxygen-depleting effect, which is of maximal significance for cells or tissues which would otherwise be partially sensitized by low levels of oxygen. (Author abstract) (19 Refs)

201. MECHANISMS OF THIOL REACTION WITH OXYGEN: IMPLICATIONS FOR HYPERTHERMIC AND RADIATION THERAPIES

Gerweck LG, Biaglow JE, Issels R, Varnes ME, Towle LR
Department of Radiology, Case Western Reserve University, Cleveland, Ohio 44106.
Adv Exp Med Biol; 180:269-80 1984

Keywords (MeSH): Cell Survival/drug effects; Comparative Study; Copper; Cysteamine; Hyperthermia, Induced; *Oxygen; Peroxides; Radiotherapy; *Sulfhydryl Compounds/toxicity.

202. LOW RADIOPROTECTION BY THIOL IN LUNG: THE ROLE OF LOCAL TISSUE OXYGENATION

Parkins C, Fowler JF, Denekamp J
Gray Laboratory of the Cancer Research Campaign, Mount Vernon Hospital, Northwood, Middlesex, U.K.
Eur J Cancer Clin Oncol; 19(8):1169-72 1983

Keywords (MeSH): Animal; Lung/*radiation effects; Male; Mice; Mice, Inbred CBA; Organothiophosphorus Compounds/*pharmacodynamics; *Oxygen Consumption; *Radiation Tolerance; Respiration; Ethiofos/*pharmacodynamics.

203. RADIOPROTECTION OF MOUSE SKIN BY WR-2721: THE CRITICAL INFLUENCE OF OXYGEN TENSION

Denekamp J, Michael BD, Rojas A, Stewart FA
Gray Lab. of the Cancer Res. Campaign, Mount Vernon Hosp., Northwood, Middlesex HA6 2RN, England
Int J Radiat Oncol Biol Phys; 8(3/4):531-534 1982

Influence of tissue oxygenation on the observed protection factor of WR-2721 was studied using the Withers epidermal clone assay. After irradiation with a continuous beam of 0.85 megaelectron volt electrons, mice were scored for the growth of macroscopic 'clones' between 12-21 days after irradiation. No difference was observed in the appearance of clones in mice irradiated with or without WR-2721. Radiosensitivity of the skin progressively decreased as oxygen concentration was reduced from 100%. Air-breathing mice were at an intermediate sensitivity, indicating a partial hypoxia of the skin. I n experiments in which 400 mg/kg WR-2721 was given 30-40 min prior to irradiation to mice breathing various oxygen concentrations, the magnitude of the protection factor changed with the oxygen tension. Max skin protection was observed when the mice breathed 50% oxygen or air. The effect of WR-2721 on the oxygen enhancement ratio (OER) for mouse skin is presented. Mice treated with WR-2721 showed a much smaller difference between the sensitivities in oxygen and nitrogen. The max OER in the presence of WR-2721 was 1.6 compared with 2.7 without drug. WR-2721 effectively shifts the max observed oxygen effect curve to the right. Data are presented which indicate the critical importance of oxygen in determining the radioprotection that can be achieved with WR-2721. Either reduced or excess oxygen can result in a diminished protection factor. (14 Refs)

204. PROTECTIVE EFFECT OF HYPOXIC MIXTURE AFTER COMBINED EXPOSURE TO RADIATION AND PHYSICAL EXERTION

Britun AI, Strelkov RB, Kucherenko NG, Kuruchkina G.
Res. Inst. Medical Radiology, Obninsk, USSR
Radiobiologiia; 22(2):250-252 1982

Radioprotective effect of hypoxic mixture (10% oxygen and 90% nitrogen) was studied in random-bred, CBA, and BALB/c mice, Wistar rats, and guinea pigs. The animals were subjected to physical exercise in combination with gamma irradiation either in the air or in the hypoxic mixture. Hypoxia resulted in significant increase of radioresistance of test animals. Exertion did not reduce the radioprotective effect of hypoxia. (13 Refs)

205. EFFECTS OF OXYGEN AND SULPHYDRYL-CONTAINING COMPOUNDS ON IRRADIATED TRANSFORMING DNA. PART I. ACTIONS OF DITHIOTHREITOL

Held KD, Harrop HA, Michael BD
Dept. Therapeutic Radiology, Mayo Clinic, Rochester, MN, 55901
Int J Radiat Biol; 40(6):613-622 1981

The actions and interactions of oxygen and the sulfhydryl-containing compound dithiothreitol (DTT) upon the radiation sensitivity of the biological activity of purified Bacillus subtilis transforming DNA have been examined. It has previously been shown that the sensitivity of transforming DNA irradiated in dilute solution is less when irradiation is performed in 100% O2 than when in 100% N2, ie O2 protects transforming DNA with a dose-modifying factor of about 0.7. DTT protects transforming DNA in a manner that is dependent on DTT concentration and on gassing conditions. In O2 the DTT protection can largely be attributed to the scavenging of-0H radicals by the DTT, but in anoxia DTT exerts a further protective effect which results in an increasing oxygen enhancement ratio (oer) with increasing DTT concentration to a max oer of about 14 at 2-5 mM DTT. This additional protective effect of DTT is attributable to hydrogen atom donation from DTT to DNA radicals, thus chemically repairing the DNA. Oxygen appears to block this chemical repair reaction. (Author abstract) (23 Refs)

206. ROLE OF ENDOGENOUS GLUTATHIONE IN RADIOPROTECTIVE EFFECT OF ANOXIA

Konstantinova MM, Minin AA, Nekrasova IV
N. K. Kol'tsov Inst. Biology of Development, Moscow, USSR
Radiobiologiia; 21(2):277-280 1981

Role of endogenous glutathione (GT) in the radioprotective effect of anoxia was studied in a culture of Ehrlich ascites carcinoma (EAC) cells. EAC cells were irradiated with 700 R either in the air or in the argon (anoxia). To decrease the level of endogenous GT, cells were incubated with N-ethylmaleimide. The radiation injury of EAC was estimated by the frequency of cells with chromosome aberrations. Binding of endogenous GT produced gradual decrease of the anoxic radioprotection. (16 Refs)

207. INDICATION OF RADIORESISTANCE MODIFIED BY RADIOPROTECTORS. COMMUNICATION 3. ANALYSIS OF THE RELATIONSHIP BETWEEN THE HYPOXIC AND RADIOPROTECTIVE EFFECTS IN BONE MARROW OF RATS

Rozhdestvenskii LM
No affiliation given
Radiobiologiia; 21(6):847-853 1981

Relationship between the hypoxic and radioprotective effects was studied in Wistar and random-bred rats. The animals were subjected to whole-body irradiation with 700 R under

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the condition of hypoxic hypoxia. Prior to irradiation, animals were injected with mexamine, epinephrine, norepinephrine, para-aminopropiophenone, or sodium nitrite. Hypoxia in the bone marrow was measured polarographically. Radioprotective effect was estimated by the cellularity of the bone marrow. It was shown that the changes in the oxygen concentration reflected the changes in bone marrow radioresistance. (18 Refs)

208. CHARACTERIZATION OF THE PROTECTIVE EFFECT OF RADIOPROTECTIVE SUBSTANCES BY MEANS OF LONG-TERM CHANGES IN OXYGEN CONSUMPTION

Mitustova J, Hosek B, Kautska J
Inst. Biophysics, Czechoslovak Acad. Sciences, Kralovopolska 135, 61265 Brno, Czechoslovakia
Strahlentherapie; 156(11):790-794 1980

A comparison of long-term hypothermic effects of radioprotective substances and their protective effectiveness was carried out in mice after acute and prolonged irradiation. Radioprotective substances used were AET, cystamine, serotonin, 5-methoxytryptamine, cysteamine-S-phosphate, sodium fluoroacetate and some double combinations of these substances. The irradiation was carried out with dose rates 38.3 and 612.5 mGy/min; the hypothermic reaction was evaluated according to total oxygen consumption, measured during 5 hr after the drug administration. The results demonstrated the existence of a correlation between the suppression of metabolic processes and both short-term and long-term protective effectiveness of radioprotective substances. The protective effectiveness of a drug is the higher; the greater decrease of oxygen consumption is induced by this substance in the investigated time interval. An analogous dependence was also demonstrated between the duration of hypothermic and radi oprotective effects. The found correlation is valid for both acute and prolonged irradiation (correlation coefficient 0.79-0.87; p less than 0.01). (Author abstract) (21 Refs)

209. RADIOLYTIC REDUCTION OF CERIC IONS IN WATER DMSO MIXTURES AND RADIOPROTECTION

Koulkes-Pujo AM, Moreau M, Sutton J
Gif Sur Yvette, France
Nature (Lond); 281(5727):128-129 1979

It is convenient to classify mechanisms of radioprotection into those that involve fast radiation chemical processes and those in which the protection is the result of changes in the cell biochemistry. In the former, the added protectors have two principal effects: OH scavenging which reduces the radiosensitized damage and fast chemical repair processes involving hydrogen donation from the protector to the target radical. Typical of the first type of protector is dimethyl sulfoxide (DMSO) because it is known to be a good OH scavenger (kOH+DMSO = 5 x 10(9) mole-1 sec(-1)). We have attempted to establish the redox properties of the OH radical adduct as well as those of H2O2 or H and HO2 radicals in water-DMSO mixtures. To this end we added to the solutions containing 0.5M H2SO4, ceric ions at concentrations varying from 2.5 x 10(-3) to 5 x 10(-2) M. The Ce4+ reduction yield was determined as a function of the DMSO content in the soln, by irradiating the mixture with gamma rays, in the presence or absence of air. The details of the experimental procedure will be given elsewhere. We report here that the yields (G) are independent of the Ce4+ concentration in the range studied and of the presence or absence of air, and depend only on the DMSO concentration. (Author abstract) (6 Refs)

210. EFFECT OF CYSTEINE, GLUTATHIONE, AND 1-P-CHLOROPHENYL-TETRAZOLE-THION-2 ON POSTRADIATION CHANGES OF THE LEVEL OF METABOLIC FREE RADICALS IN TISSUES OF ALBINO RATS

Fedorchenko VI, Kuliabko PN, Chebotarev EE
Inst. Problem Oncology, Kiev, USSR
Radiobiologiia; 19(1):67-73 1979

The radioprotective effect of cysteine (CS), glutathione (GT), and 1-p-chlorophenyltetrazole-thion-2 (CPTT) on the level of metabolic free radicals was studied in albino rats. Animals were irradiated with x-rays (650 and 750 R) and with fast neutrons (215 and 300 rads). Radioprotectors were injected 20 min prior to irradiation. Animals were sacrificed 30 min, 24, 48, 72, and 168 hr after irradiation, and the level of free radicals was assessed in the brain, bone marrow, heart, lungs, liver, spleen, kidneys, thymus, small intestine mucosa, muscles, and blood. It was found that the level of metabolic free radicals in the various tissues showed a marked decrease in the first 3 hr following irradiation with both x-rays and fast neutrons: the decrease was dose-dependent. Irradiation with x-rays caused a more pronounced decrease in the level of free radicals in the lungs, liver, spleen, and thymus, while the brain and bone marrow were more resistant to irradiation with fast neutrons. Adminis tration of radioprotectors caused marked normalization of the level of free radicals after irradiation with x-rays. (11 Refs)

211. RADIOPROTECTIVE EFFECTS OF YM-08310 ON NORMAL AND MALIGNANT TISSUES

Tsukiyama I
Dept. Radiology, Tokyo Teishin Hosp., Tokyo, Japan
Nippon Acta Radiol; 38(9):888-902 1978

The radioprotective effects of YM-08310 (S-2-(3-aminopropylamino) ethylphosphorothioic acid) on normal and malignant tissues were studied in female ICR mice (normal tissue experiments) and in isoplants of C3H/He mouse ascites mammary carcinoma (MM2: experimental tumor). The LD(50)/5 (LD50 radiation dose 5 days after irradiation) of animals treated with 400 mg/kg of YM-08310 was 1,914 rads while that of controls was 950 rads. In air-breathing animals the ED(50)/24 (radiation dose needed to induce epilation in 50% of the irradiated mice 24 days after irradiation) of YM-08310 (400 mg/kg) treated animals was 3,830 rads vs 1,834 rads in untreated controls. Under hypoxic conditions the dose was 3,426 rads and 3,197 rads, respectively. Under air-breathing conditions (4,000 rads x 1) the TRT50 (50% tumor regression time) was 6.3 days for YM-08310-treated mice vs 6.24 days for controls. Under hypoxic conditions (4,000 rads x 1) the TRT50 was 7.23 and 7.61, respectively. The results from this experiment suggest that YM-08310 was less effective for tumors than for normal tissues. (no Refs)

212. DIFFERENTIAL RADIOPROTECTION OF EUOXIC AND HYPOXIC MOUSE MAMMARY TUMORS BY A THIOPHOSPHATE COMPOUND

Utley JF, Phillips TL, Kane LJ, Wharam MD, Ware WM
Sect. Radiat. Oncol., Dept. Radiol., Univ. Calif., San Francisc
Radiology; 110(1):213-216 1974

Balb/c mice bearing sc EMT-6 mammary carcinoma were given S-2-(3-aminopropylamino) ethyl phosphorothionate (WR-2721, 500 mg/kg) prior to total body irradiation (200-2,800 R) under euoxic, hypoxic, and hyperbaric conditions, and surviving tumor cells were assayed by tissue culture. Under euoxic conditions (dose-modifying factor approx. 2) WR-2721 protected the oxygenated portion of the tumor but not chronically hypoxic cells. Acutely hypoxic cells were slightly protected. Under hyperbaric conditions there was no

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effect of the drug on cell survival. Since WR-2721 has been shown to protect normal tissues with a DMF of 2-3, it is likely that decreased protection of anoxic tumor cells will be clinically useful. (15 refs)

2.

Endogenous Substances

213. 16,16-DIMETHYL PROSTAGLANDIN E2 INDUCES RADIOPROTECTION IN MURINE INTESTINAL AND HEMATOPOIETIC STEM CELLS

Hanson WR, Ainsworth EJ
Research Section, Rush University, Presbyterian St. Luke's Medical Center, Chicago, Illinois 60612.
Radiat Res; 103(2):196-203 1985

Exogenous prostaglandins (PGs) have been shown to protect gastrointestinal mucosa, liver, and pancreas from several injurious agents, including the PG inhibitor, indomethacin. Previous studies from th is laboratory showed exogenous administration of 16,16-dimethyl (dm) PGE2 also protected mouse intestinal stem cells from radiation injury. The present study extended that observation and demonstrated that PGs given to B6D2F1 mice 1 hr before irradiation increased the shoulder of the intestinal clonogenic cell survival curve. The D0 increased from 1.10 +/- 0.09 to 1.58 +/- 0.10 Gy. PGs increased the LD50/6 from 16.3 +/- 0.41 (95% confidence limits) in controls to 20.25 +/- 0.55 Gy. The 16,16-dm PGE2 increased the hematopoietic CFU-S survival in a qualitatively similar way; the extrapolation number (n) was increased from 1.03 (0.89-1.20) to 1.40 (1.27-1.54) and the D0 increased from 0.92 (0.87-0.98) to 1.14 (1.10-1.19) Gy. A large number of human tumors secrete a variety of PGs. Our results suggest that those tumors may be, in part, protected from radiation injury.

214. THE EFFECT OF 16-16 DIMETHYL PROSTAGLANDIN E2 AND THE RADIOPROTECTOR, WR-2721 ON DNA DAMAGE AND CELL SURVIVAL IN MURINE INTESTINAL EPITHELIUM FOLLOWING IRRADIATION (MEETING ABSTRACT)

Hanson W, Grdina D, Dale P, DeLaurentiis K, Angerman J
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International Conference on Mechanisms of DNA Damage and Repair. Implications for Carcinogenesis and Risk Assessment. Poster Sessions. June 2-7, 1985, Gaithersburg, Maryland, 1985.

The mechanism of radiation protection of tissues by amino thiols such as WR-2721 [S-2-(3-aminopropylamino)ethylphosphorothioxic acid] is thought to be through the 'scavenging' of free radicals. Although the process of the interaction of sulfhydryl groups and free radicals occurs throughout the cell, the degree to which this process occurs in and near DNA is thought to be the most critical aspect of drug-induced radioprotection. Protection of intestinal stem cells from radiation injury by selected prostaglandins (PGs) has also been observed (WR Hanson and C Thomas, Radiat Res 96, 393, 1983). PGs are naturally occurring potent bioactive compounds synthesized through the cyclooxygenase pathway of the arachidonic acid cascade. Following treatment with either PGs or WR-2721, both the shoulder and the slope of the intestinal stem cell survival curve were increased. The mechanism of PG-induced radioprotection is unknown but preliminary results show: (1) PGs protected human M-1 melanoma spheroids, in part, from radiation but no protection was seen in the same cells grown as a monolayer and, (2) the combination of PGs and WR-2721 appear to be additive in their radioprotective effect, both suggest that the mechanism of PG-induced protection may be different than that associated with WR-2721. Alkaline elution was used to measure the initial DNA damage and subsequent repair rate of DNA breaks in control mice and in mice given WR-2721 or 16-16 dimethyl (dm) PGE2. WR-2721 given to mice 0.5 hr before 5-15 Gray Cesium-137 irradiation decreased the number of initial radiation-induced DNA strand breaks in intestinal tissue. In contrast, 16-16 dm PGE2 given 1 hr before 5-15 Gray irradiation (the time of PG treatment that was most radioprotective) did not alter the number of radiation-induced DNA strand breaks, nor was the rate of repair affected. Using the fluorometric application of the alkaline elution technique, the formation and subsequent rejoining of DNA single strand breaks reflect the response of all cells in the mucosa, whereas the assay for intestinal radiosensitivity is specific to only the stem cell population. Unless the PGs are specific to intestinal stem cells, the data suggest that the mechanism of radioprotection of WR-2721 and PGs may be different. These preliminary data further suggest that a non-DNA target with which PGs interact (perhaps cell membranes) may determine, in part, the radiosensitivity of cells within tissue. (1 Ref)

215. RADIOPROTECTION OF HUMAN MELANOMA SPHEROIDS BY 16-16 DIMETHYL PROSTAGLANDIN E2 (MEETING ABSTRACT)

Hanson W, DeLaurentiis K, Malkinson F
Rush-Presbyterian-St., Lukes Medical Center, Chicago, IL 60612
Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 97, 1985.

Several prostaglandins (PGs) were found to protect murine gut and marrow stem cells in vivo from radiation injury but PGs did not protect Chinese hamster ovary (CHO) cells in vitro. To test whether cell contact might, in part, account for this difference, Pg-induced radioprotection was investigated in human melanoma (M-1) grown as spheroids or as single cells. M-1 spheroids (0.2 mm diameter) were given media with or without 16-16 dimethyl (dm) PGE2 (2 ug/ml) prior to doses of 137 Cs gamma irradiation. Ten days later, tritiated thymidine (3HTdR) uptake into viable cells was assayed. Individual M-1 cells were incubated with or without 16-16 dm PGE2 (2 ug/ml) prior to radiation. Ten days later 3H uptake was assayed. PG-induced radio-protection was seen in spheroids. The surviving fraction in PG-treated spheroids was 0.95=0.06 at 5 Gy whereas the control value was 0.58=0.08 (p=0.005). No Pg-induced radioprotection was seen in M-1 cells irradiated as single cells. The results suggest that PG-induced radioprotection may be associated with cell contact. Since many human tumors secrete PGs, they may be, in part, protected from radiation treatment.

216. MODULATION OF N-ETHYL MALEIMIDE-INDUCED CELLULAR RADIOSENSITIZATION BY PROSTAGLANDIN E2 (MEETING ABSTRACT)

Holahan EV, Hagan MP, D'Alesandro M, Blakely WF
Armed Forces Radiobiology Res. Inst., Bethesda, MD 20814-5145
Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 117, 1985.

Prostaglandins (PG's) are highly active substances with a wide range of reported effects. One of the se prostaglandins, PGE-2, has been demonstrated to be a radioprotective agent for some cell lines when irradiated in vitro. We have examined the dependency of intracellular thiol content, modified by thiol binding or synthesis inhibitors, on the mechanism(s) of this cellular radioprotective effect. We treated exponentially growing synchronous and asynchronous Chinese hamster fibroblasts with both PGE-2 and N-ethyl-maleimide (NEM) to determine how PGE-2 affects cellular radiosensitivity. Chinese hamster V79-A03 cells were incubated in alpha MEM medium supplemented with 10% fetal bovine serum.

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A two hr pretreatment with 14 uM PGE-2 in medium did not radioprotect the cells from graded doses of x-rays (Do=2.0 Gy, Dq=5.7 Gy). However, when the cells were exposed to a nonspecific thiol binding radiosensitizer, 1 uM NEM in phosphate buffered saline for 30 min, PGE-2 radioprotected these cells. This radioprotection was expressed as a 0.8 to 1.3 Gy increase in the shoulder of the asynchronous radiation survival curve. This increased survival, approx 2-fold for asynchronous cells after 10 Gy, was also demonstrated in cells selected in mitosis and irradiated in G1 or S phase. Incubation in medium with 0.30 mM buthionine-S,R-sulfoximine (BSO) did not inhibit this recovery thus suggesting that this recovery might not be glutathione mediated. We are currently measuring intracellular glutathione content changes after NEM exposure with or without PGE-2 treatment using the monobromobimane derivatization-HPLC detection method and the Tietze spectrophotometric assay method utilizing the Ellman's reagent. We hope to correlate cell-cycle x-ray survival changes with free thiol content, NEM binding of thiols, and their resynthesis.

217. HUMAN MELANOMA SPHEROIDS ARE PROTECTED FROM RADIATION INJURY BY 16-16 DIMETHYL PROSTAGLANDIN E2 (MEETING ABSTRACT)

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Proc Annu Meet Am Assoc Cancer Res; 26:68 1985

Several prostaglandins (PGs) were found to protect murine gastrointestinal and hematopoietic stem cells IN VIVO from radiation injury but PGs did not protect chinese hamster ovary (CHO) cells IN VITRO. To test whether cell contact might, in part, account for this difference, PG-induced radioprotection was investigated in human melanoma (M-1) grown as spheroids or as single cells. M-1 spheroids (0.2mm diameter) were given media with or without 16-16 dimethyl (dm) PGE2 (2 ug/ml) for 2 hrs. prior to graded doses of 137Cs gamma irradiation. Eight spheroids of each group for each radiation dose were placed individually in a 48 well culture dish. Ten days later, tritiated thymidine (3HTdR) uptake into viable cells was assayed. Individual M-1 cells were incubated with or without 16-16 dm PGE2 (2 ug/ml) for 2 hrs. prior to graded doses of radiation. Eight groups of 1000 cells for each treatment for each radiation dose were placed into 48 well culture dishes. Ten days later 3H uptake was assayed. PG-induced radiation protection was seen in M1 spheroids. The surviving fraction in PG treated spheroids was 0.95 = 0.06 at 5 Gy whereas the control value was 0.58 = 0.08 (p=0.005). PG-induced radioprotection was seen in spheroids up to 20 Gy at which dose, there was no survival in either group. No PG-induced radioprotection was seen in M-1 cells irradiated as single cells. The results suggest that the mechanism of PG-induced radioprotection may be associated with cell-cell contact. Since many human tumors secrete PGs, they may be, in part, protected from radiation treatment.

218. THE ROLE OF ENDOGENOUS GLUTATHIONE IN THE ACTION OF SULFUR-CONTAINING RADIOPROTECTORS

Konstantinova MM, Minin AA, Dontsova GV, Panaeva SV

Radiobiologiia; 23(6):749-53 1983

In experiments on Ehrlich ascite tumor cells, the dependence of the radioprotective effect of beta-mercaptoethylamine and beta-mercaptopropionylglycine on the initial level of endogenous glutathione was studied. A varying degree of N-ethylmaleimide induced decrease of SH-glutathione content in the cells led to either easing or elimination of the radioprotective effect of the agents under study.

219. RADIORESISTANCE IN CELLS WITH HIGH CONTENT OF METALLOTHIONEIN

Bakka A, Johnsen AS, Endresen L, Rugstad HE

Dept. Clinical Pharmacology, Rikshospitalet, Oslo, Norway

Experientia; 38(3):381-383 1982

An endogenous cytoplasmic protein, metallothionein (MT) apparently gave rise to radioresistance in two different cell lines. A dose reduction factor of 1.9 was achieved in MT-containing cells. MT accounted for a three to four-fold increase of total sulfhydryl groups in the resistant cell strains, compared to the non-resistant lines from which they were derived. The protein is rich in cysteine (30%), an amino acid known to give radioprotection when administered exogenously. Glutathione levels and cell-cycle phase distribution showed no marked difference between resistant and corresponding non-resistant cells. (Author abstract) (18 Refs)

3.
Tumor Bed Effect

220. PROTECTION OF TUMOR BED EFFECT (TBE) AS A FACTOR IN WR-2721 INDUCED TUMOR RADIOPROTECTION (MEETING ABSTRACT)

Hunter N, Milas L, Ito H, Peters LJ

M.D. Anderson Hosp. and Tumor Inst., Houston, TX 77030

Thirty-Second Annual Meeting of the Radiation Research Society, March 25-29, 1984, Orlando, Florida, p. 38, 1984.

Many factors determine tumor radioprotection with S-2-(3-aminopropylamino)ethylphosphorothioic acid (WR-2721), including accessibility of WR-2721 to tumor cells, hypoxic state, and active absorption of the drug by tumor cells. Here we report that reduction of the modification of TBE might be an additional important factor in tumor radioprotection. C3Hf/Kam mice were irradiated to the right hind th ighs with graded doses of gamma rays ranging from 500 to 3000 rad. Approx half of the mice were given ip injections of WR-2721 at a dose of 400 mg/kg 30 min before irradiation. One day after irradiation, 4 x 10(5) MCa-4 mammary carcinoma cells were injected into the irradiated tissue. A marked TBE for this tumor was manifested by delay of tumor appearance and slowed growth rate. WR-2721 significantly reduced this effect with a protection factor (PF) higher than 1.5. This protective effect of WR-2721 is also operative in the tumor therapy setting. The growth rate of MCa-4 recurrences after local tumor irradiation was faster in WR-2721 treated mice (tumor doubling time = 15.9 +/- 1.3 days) than in mice that received irradiation only (21.2 +/- 1.7 days). MCa-4 is also protected in TCD50 assay by WR-2721 with a PF of 1.2-1.3 (Int J Rad Onc Biol Phys, 1983, in press). Thus, WR-2721 can efficiently protect against TBE, and this mechanism appears to contribute to observed tumor radioprotection. (1 Ref)

221. STROMAL RADIOSENSITIVITY: INFLUENCE OF TUMOUR TYPE ON THE TUMOUR BED EFFECT ASSAY

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Br J Radiol; 58(685):93-6 1985

Keywords (MeSH): Adenocarcinoma/pathology; Animal; Dose-Response Relationship, Radiation; Ethiofos/therapeutic use; Mice; Mice, Inbred CBA; Neoplasm Transplantation; Neoplasms, Experimental/*pathology; Radiation Injuries, Experimental/*pathology/prevention and control; Radiation Tolerance; Sarcoma/pathology.

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222. MODIFICATION OF STROMAL RADIOSENSITIVITY BY MISONIDAZOLE AND WR-2721

Begg AC, Terry NH
Gray Laboratory, Mount Vernon Hospital, Middlesex.
Br J Radiol; 56(668):565-70 1983

The radiosensitivity of normal vascular connective tissue has been assessed by measuring the growth rate of untreated tumours implanted into pre-irradiated sites. Dose response curves have been constructed from two end-points, the latent period (time for the tumours to reach a diameter of 2 mm) and the growth rate in the macroscopic range (above 4 mm). Well defined dose response curves were obtained for both end-points, with a lower dose threshold for the macroscopic growth rate. A third end-point which combined the first two was also tested, i.e., time to reach 8 mm (23 to 76 days over the dose range tested). This was found to give the steepest dose response curves overall and was therefore judged to be the best assay. Modification of the radiosensitivity of stromal tissue by misonidazole and by WR-2721 was investigated using this assay. The dose response curve for X rays plus misonidazole was similar to that for X rays alone indicating little or no radiosensitisation. WR-2721, however, significantly reduced the X-ray response indicating radioprotection by a factor of 1.8 (range 1.4-2.7). These data show that tumour implantation is an effective way of eliciting a quantifiable resp onse in previously irradiated stromal tissue. The assay allows resolution of dose differences as small as 1 to 2 Gy.

223. EFFECT OF TUMOR TYPE, SIZE, AND ENDPOINT ON TUMOR RADIOPROTECTION BY WR-2721

Milas L, Hunter N, Ito H, Peters LJ
University of Texas, M.D. Anderson Hospital and Tumor Institute, Houston.
Int J Radiat Oncol Biol Phys; 10(1):41-8 1984

Experiments are reported showing that the degree of tumor radioprotection afforded by WR-2721 varies with the type of tumor and assay endpoint, and that for a given tumor system, microaggregates are protected better than larger cell masses. The tumors used were a methylcholanthrene-induced fibrosarcoma (FSa), and two tumors of spontaneous origin, another fibrosarcoma (NFSa), and a mammary carcinoma (MCa-4), all syngeneic to C3Hf/Kam mice. WR-2721 was given in a dose of 400 mg/kg 30 minutes before irradiation in all experiments. In TCD50 assays, WR-2721 protected 5 mm diameter and impalpable 3 day-old transplants of 5 X 10(5) FSa cells growing in the leg by factors of 1.11 and 1.13, respectively. Using the tumor latency endpoint, 3 day-old s.c. transplants of 10(3) FSa in the abdominal wall were protected by a factor of 1.27, a degree of protection similar to that reported earlier for sterilization of lung micrometastases of the same tumor. MCa-4 tumors growing in the leg were protected better than FSa in TCD50 assays with protection factors of 1.3 for 4 day-old transplants, 1.24 for 5 mm tumors, and 1.23 for 8 mm tumors. MCa-4 tumors recurrent after irradiation as 4 day-old transplants grew more rapidly in mice that had received WR-2721, and this was shown to be most likely due to protection by the drug against expression of the tumor bed effect. Using the lung micrometastases assay, NFSa was protected by a factor of 1.22. This variability in protection with different tumor types, sizes, and assay endpoints is discussed in terms of drug delivery and uptake, and also in relation to the influence of tumor hypoxia on the radioprotective ability of WR-2721.

E. IMMUNOLOGICAL ASPECTS

224. PROTECTION BY S-2-(3-AMINOPROPYLAMINO)ETHYLPHOSPHOROTHIOIC ACID AGAINST RADIATION- AND CYCLOPHOSPHAMIDE-INDUCED ATTENUATION IN ANTITUMOR RESISTANCE

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Department of Experimental Radiotherapy, University of Texas M.D. Anderson Hospital and Tumor Institute at Houston.
Cancer Res; 44(6):2382-6 1984

Studies were performed to investigate whether S-2-(3-aminopropylamino)ethylphosphorothioic acid (WR-2721) can protect antitumor immune rejection responses against the damaging effects of whole-body irradiation (WBI) and cyclophosphamide (CY). Among these damaging effects were radiation-induced enhancement of s.c. tumor take and radiation- and CY-induced enhancement of lung colonization by tumor cells injected i.v. The ability of WR-2721 to protect against WBI-induced decreased radioresponse of solitary tumors was also investigated. All experiments were performed with an immunogenic fibrosarcoma syngeneic to C3Hf/ Kam mice. WR-2721 was given i.p. at a dose of 400 mg/kg 30 min before WBI with gamma-rays or CY injection. WBI with 650 rads reduced the number of tumor cells needed for tumor take in 50% of animals from 5.1 X 10(4) cells in normal mice to 2.0 X 10(2). WR-2721 given before WBI almost entirely abolished the effect of WBI: the number of tumor cells needed for tumor take in 50% of animals was 1.4 X 10(4). Treatment of mice with WBI or CY increased the number of tumor nodules in the lung generated by fibrosarcoma cells injected i.v. 5 days later, in a linear dose response. WR-2721 greatly reduced this metastasis enhancement effect of WBI and CY with protection factors of 2.5 for WBI and 1.8 for CY. Fibrosarcomas of 8 mm in diameter exhibited a decreased radiocurability when growing in WBI mice: the dose of irradiation yielding local tumor control in 50% of animals in these mice was 5950 compared to a dose of irradiation yielding local tumor control in 50% of animals of 4160 rads in normal mice. WR-2721 given before WBI inhibited this effect of WBI: the dose of irradiation yielding local tumor control in 50% of animals was 5210 rads. The proportion of macrophages in tumors growing in WBI mice was significantly reduced, but not when WR-2721 was first given. WR-2721 greatly reduced the damaging effects of WBI and CY on natural killer cell activity. Therefore, WR-2721 was capable of protecting the immune mechanisms involved in antitumor resistance against WBI and CY. This might be of therapeutic benefit when WR-2721 is combined with radio- or chemotherapy.

225. EFFECT OF SULFUR COMPOUNDS ON RADIATION-INDUCED SUPPRESSION OF DELAYED-TYPE HYPERSENSITIVITY TO OXAZOLONE IN MICE (MEETING ABSTRACT)

Weiss JF, Srinivasan V, Jacobs AJ, Rankin WA
Armed Forces Radiobiology Research Institute, Bethesda, MD 20814
Proc Annu Meet Am Assoc Cancer Res; 25:235 1984

Protection or stimulation of the immune system is an important aspect of radioprotection. Some immunomodulators that are converted to thiol derivatives may also have radioprotective properties. An in vivo method has been developed for assessing the effects of potential radioprotectants and/or immunomodulators on cell-mediated immunity in irradiated mice by measuring changes in delayed-type hypersensitivity (DTH) to oxazolone (4-ethoxymethylene-2-phenyl-oxazole-5-one). CD2F1 male mice were sensitized by applying oxazo-

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lone on the abdomen, and 3 days later the animals were irradiated (cobalt-60, 700 rads). Two days after irradiation, a challenge dose of oxazolone was applied to one ear and vehicle only to the opposite ear; DTH (difference in ear thicknesses) was measured after 24 and 48 hr. Drugs were injected IP in saline (pH 6-8) at half the LD10 or maximum tolerated dose, approx. 1/2 hr before irradiation. Of the compounds tested, WR-2721, SA-2-(3-aminopropylamino)-ethylphosphorothioic acid, provided the best protection of the DTH response. The DTH response in irradiated, saline treated mice was 40% of that in nonirradiated groups, whereas the response was 75% of normal in groups treated with WR-2721 (400 mg/kg). Slightly less protection was afforded by 2-mercaptoethylamine (200 mg/kg), S-(2-aminoethyl)isothiouronium-Br-Hbr (200 mg/kg), or glutathione (1 g/kg). Protection was also significant due to treatment with diethyldithiocarbamate (800 mg/kg) or mercaptopropionyl glycine (800 mg/kg), and levamisole (20 mg/kg) gave the least protection. Although the specific mechanism of protection (such as protection of lymphocytes and/or macrophages) is not known, this procedure appears to be useful for the comparative assessment of drugs in protecting against radiation-induced decrements in cellular immunity.

226. INFLUENCE OF THE IMMUNOMODULATING COMPOUND BM 12.531 (AZIMEXONE) ON RADIORESISTANCE AND GRANULOPOIETIC COLONY FORMING UNITS IN MICE

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Exp Pathol; 20(2):105-107 1981

BM 12.531 (azimexone) increases the survival of mice exposed to 650 rad. Levamisole, isoprenosine or aristolochia acid have no effects in this system. After administration of 25 mg/kg azimexone to C57 Bl/6-mice, a statistically significant increase in CFUc was found. This increase in CFUc may explain the radioprotective effect of azimexone. (Author abstract) (12 Refs)

227. ON THE RADIOPROTECTIVE ACTIVITY OF LIPIDS

Tumanjan MA, Duplisceva AP, Sinilova NG, Serebrennikova GA, Klykov VN, Mitrofanova TK
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Radiobiol Radiother (Berl); 22(3):324-330 1981

Several derivatives of neutral lipids and phospholipids were tested for radioprotective activity in male white mice. Mice received lipid treatment 24 hr prior to irradiation. Radiation dose was 8.50 Gray (LD100/30) or 7.25-7.50 Gray (LD50/30). Effects of the preparations tested were measured by survival time and by the resistance of mice to infection with Salmonella typhimurium. Most of the lipids tested protected the mice, yielding a 10-25% survival rate compared with 6% for controls at LD90/30. Neutral lipid activity was not affected by the presence of an oxygen, a double bond, or two double bonds in the lipid molecule. Cis- and trans-isomers had equal effect. Compounds with double bonds in the 9 and 12 positions were less active than those with double bonds in the 1 and 9 positions. Cholesterin derivatives had activities similar to neutral lipids. Lengthening of side chains or presenc e of double bonds in the side chains had no effect. Phospholipids had a somewhat higher activity than neutral lipids. Natural and synthetic preparations of cephalin and lecithin had similar activities. All tested compound increased resistance to S typhimurium. Neutral lipids with saturated alcohols had the greatest effect. Those with two double bonds and phospholipids had lesser effects. Results suggest that lipids are stimulants of natural immunity. (10 Refs)

228. USE OF BCG VACCINE AS RADIOPROTECTOR

Bestuzheva GR, Aldzhambaev Shlu, Mustafina FS
Dept. Microbiology, Kirgiz Medical Inst., Frunze, USSR
Probl Tuberk; (7):46-50 1981

The results of experimental and clinical trials of radioprotective properties of BCG vaccine are reported. Immunization of guinea pigs prior to irradiation with 300 R increased the nonspecific immunity and reduced the lethality (36%, compared with 55% in irradiated controls). The adjuvant immunotherapy was used in 23 patients with cervix carcinoma. Administration of BCG vaccine (0.005 mg, sc) 1-2 days prior to irradiation increased lysozyme level and stimulated the phagocytosis. Immunostimulating effect of BCG vaccine was more pronounced in the patients with Stage II. (20 Refs)

229. RADIOPROTECTIVE EFFECTIVENESS OF THE PARAMUNITY INDUCER 'PIND-AVI': INVESTIGATION USING THE MODEL 'PROTECTIVE TETANIC VACCINATION IN MICE' AFTER EXPOSURE TO X-RAYS

Mayr A, Baljer G, Sailer J, Schels D
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Strahlentherapie; 156(11):795-799 1980

The model 'protective tetanic vaccination in mice' was used in order to try whether the paramunity inducer Pind-Avi may diminish or suspend radiation-induced immunosuppression. The radioprotective effect was ascertained from the different results of immunization in mice exposed to radiation after pretreatment with either Pind-Avi or placebo. The dose delivered amounted to 300 R. Tetanus toxoid was used for immunization. Effectiveness of the tetanic vaccination was analyzed by means of load tests with 10 LD50 tetanus toxin, and of antibody determination with passive hemagglutination. Evidence was shown of significant radiation protection following sc application of Pind-Avi once a day during 3 days before of after exposure. Efficiency in mice treated with Pind Avi amounted to 75% (pre-irradiation treatment) and to 43% (postirradiation treatment), whereas the efficiency in controls was zero in all cases. Thus, it was possible with Pind-Avi to suspend radiation-induced immunosuppression within a period of 3 days before or after radiation exposure, not only by means of prophylactic but also by therapeutic administration. (Author abstract) (22 Refs)

230. PROTECTIVE EFFECTS OF INTERFERON IN MICE PREVIOUSLY EXPOSED TO LETHAL IRRADIATION

Ortaldo JR, McCoy JL
Lab. Immunodiagnosis, NCI, NIH, Bethesda, MD, 20205
Radiat Res; 81(2):262-266 1980

In vivo radioprotective effects of interferon (IF) in lethally-irradiated mice were studied. BALB/c mice received 650 or 700 rads of x-irradiation 24 hr before injection of 30,000 units of partially purified mouse IF. The mean survival of irradiated mice that received no IF was 5.5 days; those of IF-treated mice after irradiation with 650 or 700 rads were 9.1 and 8.9 days, respectively. Injection of the mice with IF on 3 days (days 1, 3, and 5 after irradiation) produced only a slight increase in survival time over that produced by only one dose of IF. In order to examine some possible relevant immunological parameters, paired IF-treated and untreated mice were sacrificed 3 days postirradiation and their spleen cell numbers, peripheral WBC counts, and natural killer cell activities were determined. The peripheral WBC counts were normal

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in all animals; the spleen cell numbers in either the IF-treated irradiated mice or the untreated irradiated mice were 10- to 20-fold lower than those in the unirradiated mice. The spleen cells from the IF-treated irradiated mice had detectable natural killer activity on day 3, whereas those from the untreated irradiated mice had none. It was concluded that these results could have implications in the treatment of cancer patientr receiving high-dore radiotherapy and in individuals accidentally exposed to high doses of x-irradiation. (10 Refs)

231. EVALUATION OF A NUCLEASE-RESISTANT DERIVATIVE OF POLY(I).POLY(C) [POLY(ICLC)] AS A RADIOPROTECTIVE AGENT

Baze WB, Lvovksy E, Higbee GA, Levy HB, Hilmas DE
United States Army Medical Res., Inst. Infectious Disease, Fort Detrick, Frederick, MD, 21701
Radiat Res; 77(2):276-284 1979

A study was made of the radioprotective effect of a stabilized complex of polyriboinosinic acid, polyribocytidylic acid, poly-L-lysine, and carboxymethylcellulose (polyICLC) in mice subjected to whole-body irradiation. Doses of 0.1-3 mg/kg of polyICLC were injected im into randomly selected male Swiss-Webster mice either as a single dose 8, 24, 48 or 72 hr before irradiation or as two doses 24 and 48 hr or three doses 24, 48 and 72 hr before irradiation (400-1000 rad). Pretreatment with polyICLC increased significantly the 30 day survival rate (p less than 0.05) when the irradiation dose was in the 600-800 rad range. The max protective effect occurred when polyICLC was given as a single dose 48-72 hr before irradiation or in mutiple doses. Serum interferon titers were max 24 hr after but barely detectable 48 and 72 hr after the injection of the first drug dose. Dosages over 3 mg/kg did not produce an increase in protection, although interferon titers increased with increasing doses. PolyICLC had a slightly stimulatory effect on the numbers of peripheral blood elements in irradiated mice. The use of polyICLC as a chemotherapeutic and radioprotective agent in cancer therapy should be explored. (31 Refs)

232. RADIOPROTECTION OF IMMUNOLOGICALLY REACTIVE T LYMPHOCYTES BY WR-2721

Harris JW, Menezes JJ
Lab. Radiobiology LR104, Univ. California, San Francisco, CA, 94143
Int J Radiat Oncol Biol Phys; 4(5/6):437-440 1978

The in vivo radioprotective effects of S-2-(3-aminopropylamino) ethyl phosphorothioic acid (WR-2721) on murine splenic T lymphocytes, which form cytolytic T lymphocytes (CTL) in mixed leukocyte culture (MLC), were investigated. C57Bl/6 female mice were injected ip with 400 mg/kg WR-2721 20 min before irradiation at a dose rate of 85 rads/min. MLC were prepared with irradiated spleen cells from DBA/2 mice and with spleen cells from the experimental C57Bl/6 mice; MLC were incubated for 4 days. CTL were measured by Cr51 release from P815 mastocytoma cells. Viable cells were measured by exclusion of trypan blue dye. WR-2721 protected both viable cell recovery and CTL activity. The WR-2721 dose-modifying factor (DMF) at 10% survival for viable cells recovered from animals irradiated with greater than 200 rads was 1.60. The response curves for cytolytic activity were more complex than those for viable cell recovery, varying with the dose of radiation given. At doses up to 300 rads, cytolytic activity increased above that of unirradiated controls: for WR-271-protected cells, 2.7-fold; for unprotected cells, 1.5-fold. The WR-2721 DMF for cytolytic activity was 1.80 at radiation doses up to 300 rad, and was 1.69 (at 10% survival) at greater than or equal to 300 rads (1.54 if the slopes rather than activities were compared). WR-2721 gave no radioprotection if it was given 2 min before irradiation, but gave full protection if given 10 min before. A high degree of protection lasted for at least 90 min after injection. WR-2721 provides radioprotection for those splenic T lymphocytes that respond to alloantigen by differentiating into immunologically specific CTL. WR-2721 might be of benefit in protecting the immune system in patients undergoing radiotherapy. (20 Refs)

233. RADIOPROTECTIVE ACTIVITY OF INTERFERON INDUCERS

Talas M, Szolgay E
Microbiological Res. Group, Hungarian Acad. Sciences, Piheno ut 1, 1529 Budapest, Hungary
Arch Virol; 56(4):309-315 1978

The radioprotective activity of interferon inducers (tilorone, Acranil, polyinosinic acid: cytidylic acid and Escherichia coli lipopolysaccharide) against acute x-ray irradiation and prolonged 60Co-gamma ray irradiation was investigated. The endogenous spleen colony formation test and percentage of surviving mice 30 days after irradiation were used as indicators. All interferon inducers investigated proved to have radioprotective activity. (Author abstract) (34 Refs)

IV.

PHARMACODYNAMICS AND METABOLISM OF RADIOPROTECTORS

234. HUMAN PHARMACOKINETICS OF WR2721 (MEETING ABSTRACT)

Shaw LM, Turrisi A, Glover D, Bonner H, Norfleet AL, Glick J, Kligerman M
Dept. of Pathology and Lab. Medicine, Univ. of Pennsylvania, Philadelphia, PA 19104
Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-23, 1985.

For measurement of WR2721 in plasma and its free sulfhydryl metabolite in whole blood a sensitive and specific electrochemical HPLC procedure was used [Shaw, LM, et al J Liq Chrom 7 2447-2465 (1984)]. A series of patients (pts) (N=13) studied were given 150 mg/M2 of WR2721 as an iv bolus administered in 10 seconds. Concentration versus time data were fitted to standard pharmacokinetic models using nonlinear least squares analysis. At the 150 mg/M2 dosage only small concentrations of WR1065 appear in pt's blood (up to 20 umol/L). However, greater concentrations of WR1065 appear in the blood of pts given larger WR2721 doses. The distribution (alpha) phase of the pharmacokinetic curves is predominant for each of the pts accounting for most of the disappearance from blood whereas the elimination (beta) phase is much less significant and in fact not present in four of pts. Renal excretion of WR2721 and WR1065 was monitored during the one hr post-injection study period in 6 of the pts. WR2721 and WR1065 urinary excretion were minimal, ranging from 0.23 to 1.43% of the administered dose for WR2721 and from 0.25 to 9.7% for WR1065. The very short av distribution T1/2 of 0.87 min, the small av central compartment vol of distribution of 0.10 L/Kg and the finding that little drug is excreted in the pts' urine suggest that the drug leaves the bloodstream very rapidly to enter tissues where it is rapidly converted to metabolite(s). (1 Ref)

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235. **PHARMACOKINETICS OF ETHIOFOS (WR 2721) IN THE RHESUS MONKEY (MEETING ABSTRACT)**
Suynnerton NF, Mangold J, Ludden TM
Southwest Res. Inst., San Antonio, TX
Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-21, 1985.

Development of a suitable oral dosage form of the radioprotectant drug ethiofos (WR 2721) required background information on the kinetic behavior of the drug following IV administration to animal models. The drug was infused at a concentration of 100 mg/mL in normal saline solution over ten min to 5 young Rhesus monkeys weighing 3 to 5 kg. Following a dose of 120-150 mg per kg body wt, plasma concentrations of unchanged drug were measured using HPLC with derivatization and fluorescence detection. Concentrations of the drug ranged from 477 ug/mL (2.23 mM) to the detectable limit of 0.05 ug/mL (0.23 uM) in two to three hr postinfusion. Clearances calculated from the ratio of dose to area under the plasma concentration time curves averaged 43.5 +/- 13.4 (SD) mL min-1 kg-1. Half-lives observed in the 20-60 min postinfusion were 8-15 min. At times exceeding 60 min after the end of infusion th ere was evidence of either a recycling process or time dependent kinetics. Ethiofos concentrations varied erratically between 0.05 and 0.5 ug/mL in this period.

236. **PHARMACOKINETICS OF S-2-(3-AMINOPROPYLAMINO)-ETHANE THIOL (WR 1065) IN THE BEAGLE DOG FOLLOWING INTRAVENOUS ADMINISTRATION (MEETING ABSTRACT)**
Mangold DJ, McGovern EP, Huelle BK, Suynnerton NF, Ludden T
Southwest Res. Inst., San Antonio, TX 78230
Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 97, 1985.

The pharmacokinetics in the beagle dog following iv infusion over 10 min (39 mg/kg) of S-2-(3-aminopropylamino)ethane thiol, a metabolite of the radioprotective drug ethiofos has been determined. The analyte is separated using HPLC and quantified with a specific amperometric detector employing a Hg/Au working electrode. Plasma levels observed immediately following the completion of the infusion ranged from 25 to 42 g/mL (three animals) but rapidly decreased within 60 min to approx 1.0 g/mL and approached the analytical method detection limit of 0.05 g/mL after 6 hr. The mean central compartment volume was 0.82 L kg(-1), n=3, the mean elimination clearance was 0.049 L min(-1) kg(-1) and the mean terminal half life was 1.1 to 1.8 hr, which was longer than for ethiofos. The plasma concentration versus time profiles for three animals are best described by a three compartment pharmacokinetic model.

237. **WR2721 AND WR1065 PHARMACOKINETICS IN MICE (MEETING ABSTRACT)**
Shaw LM, Brown DQ, Bonner HS, Coia L
Dept. of Pathology and Lab. Medicine, Univ. of Pennsylvania, Philadelphia, PA 19104
Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-19, 1985.

Tissue distribution of WR2721 and its free sulfhydryl metabolite, WR1065, after intraperitoneal injection of WR2721 (365 mg/Kg) was investigated. WR2721 and WR1065 concentrations were measured in whole blood and tissues using newly developed electrochemical HPLC methods and specimen preparation technique that assures accurate measurement of both WR2721 and WR1065 [Shaw, LM, et al, (a) J Liq Chrom 7 2447-2465 (1984) and (b) in press]. The tissue WR1065 concentration versus time patterns showed interesting differences: peak WR1065 concentrations were obtained in blood, liver and kidney 10 min after WR2721 administration. In contrast to this, WR1065 concentrations steadily increased in heart and tumor with the highest concentrations occurring at 30 min after WR2721 injection. Data are consistent with the suggestion that the time after WR2721 administration at which radioprotection will be optimal (ie the time at which the highest tissue concentrations of WR1065, and possibly its metabolites, occur) will vary from tissue to tissue. Tissue concentrations of WR2721 were generally much lower than the corresponding WR1065 concentrations with the exception of EMT6 tumor. At 10 min after WR2721 administration the tumor concentration of WR2721, 127 nmol/g, was twice that of WR1065 (62 nmol/g). In order to test the hypothesis that alkaline phosphatase catalyzes the dephosphorylation of WR2721 to produce WR1065 in vivo, mice bearing the EMT6 tumor were injected subcutaneously with 75 mg/Kg of the alkaline phosphatase inhibitor levamisole 10 min before intraperitoneal injection of 365 mg/Kg WR2721. WR1065 tissue concentrations, except for that in the EMT6 tumor, were reduced by the alkaline phosphatase inhibitor levamisole. The fact that EMT6 tumor WR1065 concentrations were unchanged suggests that the mechanism for WR1065 production and entry into tumor cells may be different from that of other tissues. (1 Ref)

238. **COMPARATIVE BIODISTRIBUTION OF THREE RADIOPROTECTORS: WR-2721, WR-77913, AND WR-3689 (MEETING ABSTRACT)**
Rasey JS, Grunbaum Z, Krohn KA, Menard TW, Spence AM
Univ. of Washington, Seattle, WA 98195
Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 44, 1985.

The biodistribution of S-35 labeled WR-2721, WR-77913, and WR-3689, expressed as % injected dose/g (%ID/g), was compared after ip injection of radioprotective doses in C3H mice bearing RIF-1 tumors. Blood levels peaked at 10 min for WR-2721 (0.64% ID/g) and WR-77913 (2.80% ID/g), and at 15 min after injection for WR-3689 (1.78% ID/g). S-35 from WR-77913 and WR-3689 was highest in most tissues at 15 or 30 min post injection, while S-35-WR-2721 reached highest levels in most tissues only after 30-60 min. At 30 min high levels of all three drugs were found in submandibular salivary gland (4.02 to 6.95% ID/g) and kidney (3.45 to 6.34% ID/g), with lowest levels in brain (0.10 to 0.26% ID/g) and slightly higher levels in tumor and skin. At that time, uptake of WR-3689 in lung nearly as great as in kidney, and uptake of WR-77913 by gut was nearly as high as kidney levels. The three protectors show similarities of organ distribution but different time courses in achieving maximum levels or in retaining drug. H-3-WR-3689 has been used in diffusable substance autoradiography to demonstrate the subcellular distribution of label. This, and the biodistribution data, will aid in interpreting radioprotection studies.

239. **IN VIVO AND IN VITRO DETECTION OF THE RADIATION PROTECTOR WR-2721 USING 31P NMR (MEETING ABSTRACT)**
Sridhar R, Crossley C, Robinson RD, Schmidt PG
Oklahoma Medical Res. Foundation, Oklahoma City, OH 73104
Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 98, 1985.

The presence of S-2-(3-aminopropylamino)ethyl-phosphorothioic acid (WR-2721) and its dephosphorylation in tissues and tumor can be monitored both in vitro and in vivo by phosphorus-31 nuclear magnetic resonance (31 P NMR) spectroscopy. WR-2721 was given at a dose of 400 mg/kg to a Balb/c mouse by in tramuscular injection into the thigh. Similarly, the same dose of WR-2721 was injected intratumorally into

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an EMT6 tumor growing in the hind leg of a Balb/c mouse. The muscle and the tumor were monitored at the point of injection using a surface coil to measure the 31P NMR spectra before and at 20, 40 and 80 min after drug administration. The phosphorothioate signal was clearly seen in all spectra recorded after administering WR-2721. This signal which was most intense in the spectra acquired at 20 min after drug injection, decreased progressively in the spectra acquired at later times. The rate of loss of thiophosphate signal from the poorly vascularized tumor was markedly slower compared to that from well vascularized muscle. In the case of tumor, the loss of WR-2721 signal was accompanied by simultaneous increase in inorganic phosphate signal. Such an increase in inorganic phosphate was not seen in the spectra from muscle.

240. RADIOPROTECTION OF V79 CELLS BY WR2721 AND METABOLITES IN VITRO (MEETING ABSTRACT)

Calabro-Jones P, Ward JF, Fahey RC, Smoluk G, Aguilera J
UC San Diego, La Jolla, CA 92093
Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 43, 1985

Incubation of V79-171 cells in vitro with WR2721 does not lead to their radioprotection or the accumulation of drug intracellularly. The addition of alkaline phosphatase (AP) during pre-irradiation incubation with WR2721 leads to: (a) rapid production of the thiol (WR1065) and disulfide drug forms in the extracellular medium, (b) time-dependent cellular accumulation of WR1065 and disulfides, which accompanies (c) time-dependent appearance of radioprotection. Using purified enzyme for drug 'activation' allowed quantitative and highly reproducible clonogenic determinations of the time-dose parameters required for in vitro radioprotection, ie, pre-irradiation incubation at 4mM WR2721 + AP for 1 hr yields a dose independent DMF=2.8 under oxic conditions. This radioprotection is comparable to maximum levels achieved in vivo. Tandem studies using HPLC analysis (Fahey et al, 1983) permitted the simultaneous quantitative determination of the intracellular and extracellular drug forms with accompany the appearance of radioprotection in V79-171 in vitro. The relationship(s) among intracellular drug forms and observed radioprotection were discussed in terms of possible mechanism(s) for WR2721 radioprotection. (1 Ref)

241. THE EFFECT OF RADIOPROTECTORS ON THE RADIORESPONSE OF CHO CELLS EXPOSED TO IODINATED CONTRAST MEDIUM (MEETING ABSTRACT)

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Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 44, 1985.

The use of iodinated contrast medium (ICM) is necessary in many diagnostic procedures in order to visualize anatomic structures. ICM causes an increase in absorbed dose due to the increased photoelectric effect, presenting a dilemma in that to get better diagnostic information one also gets increased radiation cytotoxicity. A significant increase in cell kill can be measured, by a clonogenic assay, when cells are irradiated in the presence of 4% ICM (19 mg I/ml) with x-ray beams with an effective energy of 30-50 KeV. Dose enhancement factors as measured by the ratios of the slopes of the survival curves, range from 1.6 to 1.8. The present study investigates the feasibility of using radioprotectants as a means of preventing this dose enhancement. The effect(s) of the addition of several radioprotective agents WR-2721, DMSO, and Vitamin E was evaluated. For example, a 10 mM concentration of WR-2721 was found to virtually eliminate this enhanced killing. The combination of radioprotectants and ICM in diagnostic procedures may prove useful in reducing the hazards, such as carcinogenesis and mutagenesis, associated with many of these procedures.

242. ALTERATIONS IN OXYGEN TRANSPORT FOLLOWING WR-2721

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Int J Radiat Oncol Biol Phys; 10(9):1565-8 1984

The toxicity of radiation and alkylating agent chemotherapy is in part related to free radical formation in DNA and associated proteins, which is enhanced by oxygen and other electron affinic compounds. During the Phase I clinical trials of WR-2721 and alkylating agent chemotherapy, venous blood samples were obtained prior to and immediately following the WR-2721 infusion. We have observed a marked increase in the oxygen saturation of venous blood following WR-2721 (430-910 mg/m2 at a rate of 15 mg/m2/minute). The mean venous PO2 (PvO2) rose from a baseline of 34.0 +/- 13.54 torr to a mean value of 54.60 +/- 12.47 torr (p less than 0.001). The percent venous oxygen saturation increased from 54.52 +/- 21.38% to 82.73 +/- 7.66%. The highest values generally occurred within the first 2 hours after the completion of the WR-2721 infusion. No significant differences were found between the pre and post WR-2721 values for either the venous pH, CO2, or bicarbonate levels. Despite increased PvO2, the patients' heart rates, blood pressures, or respiratory rates did not change pre and post WR-2721. No apparent differences were noted in the effects of WR-2721 or PvO2 when given at doses of 740 or 910 mg/m2. However, when WR-2721 (418-1100 mg/m2) was administered over 15 minutes, the PvO2 increased in only 8/13 courses. We postulated that the marked increase in venous blood oxygen concentration was secondary to one of the following mechanisms: 1) Increased affinity of hemoglobin for oxygen, 2) microcirculatory shunting, or 3) decreased tissue requirements for oxygen. In 12 patients oxygen-hemoglobin dissociation curves and intracellular red cell pH's were obtained before and after 740-910 mg/m2 of WR-2721. Despite the significant increase in oxygenation of venous blood after WR-2721, there were no changes in either oxygen-hemoglobin dissociation or intracellular red cell pH to account for this increase. The oxygen consumption of peripheral blood granulocytes was measured prior to and following 15 courses of WR-2721. A marked decrease in granulocyte oxygen consumption was observed in 6/8 patients who had a significant increase in PvO2 and only 1/7 patients who had either a decrease or no change in PvO2 after WR-2721. Our preliminary investigations suggest that the increased venous blood oxygen content may be secondary to a reduction in normal tissue oxygen consumption. WR-2721 may afford protection by both decreasing oxygen consumption and delivery to normal tissues and increasing intracellular sulfhydryls.

243. CHEMICAL INHIBITION OF HOST TOXICITY AS A MEANS OF OVERCOMING TUMOR RESISTANCE

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Biological Bases and Clinical Implications of Tumor Radioresistance. Fletcher GH, Nervi C, Withers HR, eds. New York, Masson Publishing, p. 317-29, 1986

Well-tolerated doses of S-2 (3-aminopropylamino)ethylphosphorothioic acid (WR-2721) selectively protected the hematopoietic tissues, skin, intestinal epithelium, and other normal tissues and functions against radiation (RT) damage in mice, rats, dogs, rabbits, guinea

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pigs, and monkeys. It was not a highly efficient protector of the lung or vasculature, and did not cross the blood-brain barrier to protect the CNS. In rats and mice, WR-2721 selectively protected normal tissues (bone marrow and kidney) against toxic doses of cis-diamminodichloroplatinum(II), cyclophosphamide, nitrogen mustard, or melphalan. In tumor-bearing rats or mice, WR-2721 (200 mg/kg, ip) did not protect the tumors against the toxic effects of RT or alkylating agents of RT or chemotherapy was given 30 min after protective metabolites of WR-2721 were cleared from the circulation. WR-2721 did not protect artificial micrometastases of transplanted tumors against alkylating agent toxicity. WR-2721 was passively absorbed across the cell membrane of normal tissues. Observed effects of WR-2721 included a facilitated diffusion process, dephosphorylation, an acid phosphatase-catalyzed binding to endogenous 'reporter' proteins and a temperature-dependent active concentration within the cells. A similar active concentration of WR-2721 was observed in normal human skin in vitro, but not in osteogenic sarcoma specimens from the same patient. In one Phase I clinical trial, 400 mg/m2 of WR-2721 and 100 mg/m2/wk x 3 wk were well tolerated. In another clinical study, however, 100 mg/m2 of WR-2721 caused dose-limiting hypotension. The max tolerated dose, chronic toxicity, and usefulness of WR-2721 in combination with RT or chemotherapy require further clinical testing. (25 Refs)

244. PHARMACOKINETICS OF WR-1065 IN MOUSE TISSUE FOLLOWING TREATMENT WITH WR-2721

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Int J Radiat Oncol Biol Phys; 10(9):1525-8 1984

Levels of reduced glutathione (GSH) and N-(2-mercaptoethyl)-1,3-diaminopropane (WR-1065) were measured in tissues of Balb/c mouse bearing EMT6 tumors at time intervals ranging from 5 min to 48 hr after i.v. injection of S-2-(3-aminopropylamino)ethyl phosphorothioate (WR-2721) at 500 mg per kg. In all tissues examined (liver, kidney, lung, heart, muscle, brain, tumor, spleen, and salivary gland), maximal WR-1065 levels occurred 5-15 min after injection, with levels in liver, kidney, lung, and salivary gland exceeding one mumole per gm. The post-maximum decline in WR-1065 varied markedly with tissue, lung exhibiting a 6-fold drop by 30 min and salivary gland falling only 15% after 3 hr. In a mouse treated with carbon-14 labeled WR-2721 it was found after 15 min that WR-1065 accounted for over half of the total drug in all tissues except tumor, where it accounted for a third of the total drug. There was no evidence that GSH levels were substantially altered by WR-2721 treatment. The results provide the first direct evidence supporting the widely held view that WR-2721 treatment results in intracellular WR-1065 and they demonstrate that high levels of WR-1065 occur very soon after i.v. injection.

245. DEPHOSPHORYLATION OF WR-2721 WITH MOUSE TISSUE HOMOGENATES

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Int J Radiat Oncol Biol Phys; 10(9):1529-31 1984

Mouse liver homogenate had an optimum pH of 8.6 to 8.8 for dephosphorylation of WR-2721 in the analyzed pH range from 5.2 to 10.0. At this optimum pH condition, the dephosphorylation activities of six mouse tissue homogenates were analyzed. Kidney, liver and small intestine homogenates showed higher dephosphorylation activities (935, 336 and 314 nmoles/mg protein/hr, respectively) than spleen and lung homogenates (86, 49 nmoles/mg protein/hr, respectively). Furthermore, serum did not show any dephosphorylation activity. The high activity found in liver homogenate agrees well with our previous data with mouse L cells. However, optimum pH from 8.6 to 8.8 in liver homogenate is quite different from the data reported by using Ehrlich ascites tumor cells (optimum pH was 5.6). Therefore, it is suggested that WR-2721 administered into mouse is efficiently dephosphorylated in certain tissues such as liver to its active form with the enzyme(s) different from that found in Ehrlich ascites tumor cells.

246. PROTECTION OF CULTURED MAMMALIAN CELLS BY S-2-(3-AMINOPROPYLAMINO)ETHYLPHOSPHOROTHIOIC ACID(WR-2721)

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Int J Radiat Oncol Biol Phys; 9(10):1481-5 1983

The ability of WR-2721 to protect cultured mammalian cells against radiation-induced killing was nearly the same as that of cysteamine when WR-2721 was activated by mouse liver extract. Without the liver extract, protection by WR-2721 required long incubations with the cells prior to irradiation. The protective activity increased in proportion to the cell concentration. The dose reduction factor at a concentration of 4 mM WR-2721 was 1.11 and 1.41 for 1.5 X 10(5) cells/ml and 15 X 10(5) cells/ml of cultured cells, respectively. A non-protein bound sulfhydryl group was detected in cell suspensions after incubation with WR-2721, but it was not a dephosphorylated product of WR-2721.

247. BIODISTRIBUTION OF THE RADIOPROTECTIVE DRUG 35S-LABELED 3-AMINO-2-HYDROXYPROPYL PHOSPHOROTHIOATE (WR77913)

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Radiat Res; 102(1):130-7 1985

3-Amino-2-hydroxypropyl phosphorothioate (WR77913), a less toxic phosphorothioate radioprotector than WR2721, has been labeled with 35S. The biodistribution of a radioprotective dose of 800 mg/kg was determined in C3H mice bearing RIF-1 tumors as a function of time after intraperitoneal injection and was expressed as percentage injected dose/gram (% ID/g). Levels of 35S in the blood peaked 10 min after injection, and radioactivity in most tissues was highest at 15 min. Label in most tissues declined markedly between 15 and 60 min, but in gut, salivary glands, tumor, and brain, the levels of radioactivity remained quite stable over 1 hr. At 30 min after injection the highest levels of labeled drug were found in submandibular salivary glands, gut, and kidney, with the lowest level in brain. Tumors had approximately the same amount of label as blood, muscle, skin, and esophagus. Two principal differences between the distribution of label from WR77913 and WR2721 were defined. Although blood levels of 35S-WR2721 also peaked 10 min after injection, the 10-min blood levels achieved for WR77913 were more than fourfold greater than those attained by WR2721. Maximum levels of WR2721 occurred in most tissues 30 to 60 min after administration of the drug, compared to 15 min for WR77913. The basis for these differences remains to be determined, but these results suggest that the optimum interval between administration of WR77913 and irradiation may be shorter than for WR2721.

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248. RADIOPROTECTION OF NORMAL TISSUES AGAINST GAMMA RAYS AND CYCLOTRON NEUTRONS WITH WR-2721: LD50 STUDIES AND 35S-WR-2721 BIODISTRIBUTION

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Department of Radiation Oncology, School of Medicine, University of Washington, Seattle.

Radiat Res; 97(3):598-607 1984

The ability of WR-2721 to protect mice against two modes of death following whole-body radiation with 137Cs gamma rays or d(22)+Be neutrons was examined. For single fractions, 400 mg/kg WR-2721 was administered prior to irradiation. In two-fraction exposures, the dose was 275 mg/kg given prior to each fraction. Dose modification factors (DMFs) were calculated as ratios of LD50 values. For single fractions of gamma rays, the DMF was 1.74 for the LD50/7 end point and for LD50/30, the DMF for single fractions was 2.25. For two fractions 3 hr apart, it was 1.88. For single fractions of cyclotron neutrons, the DMF was 1.32 for LD50/7. Measured with the LD50/30 end point, the DMF for single neutron doses was 1.41 and for two fractions, 1.19. Substantial radioprotection of bone marrow and intestinal epithelium against cyclotron neutrons was seen in these investigations. Biodistribution studies were done following ip injection of 35S-labeled WR-2721 into C3H mice bearing RIF-1 tumors. Blood levels peaked at 10 min after injection and declined thereafter. Most normal tissues achieved maximum levels of 35S at 30 to 60 min postinjection and high concentrations were retained in most tissues for up to 2 hr. Assuming that all 35S is in parent compound or dephosphorylated radioprotective metabolites, the concentration of protector (milligram per gram tissue) in various organs at 30 min postinjection ranked as follows: kidney greater than submandibular gland much greater than liver = lung greater than gut greater than heart much greater than blood greater than skin greater than tumor greater than brain. High levels of 35S were achieved and retention times were long in certain normal tissues which respond at early or late times postradiation and may be dose limiting in radiotherapy: kidney, liver, salivary gland, and lung. These combined observations suggest that there is potential for protecting dose-limiting, late-responding normal tissue in the radiotherapy of human cancer with both neutrons and conventional radiotherapy.

249. VARIATION IN NORMAL TISSUE RESPONSIVENESS TO WR-2721

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Int J Radiat Oncol Biol Phys; 10(9):1537-9 1984

The radioprotection afforded normal tissues by WR-2721 or S-2-[3-aminopropylamino]ethylphosphorothioic acid varies widely, with some of the most responsive tissues showing low levels of absorbed drug and vice versa. While the oxygen tension of the respective tissues may be contributing to this variation, it can be shown that the drug is not homogeneously distributed within each tissue, and that its location within the sub-cellular compartments can vary widely. Recognition of this variability, wh en combined with the newly developed HPLC assays for drug quality, should provide new insights into the sources of variation in normal tissue responsiveness to these agents.

250. DIFFERENTIAL RADIOPROTECTION OF NORMAL TISSUES BY HYDROPHILIC CHEMICAL PROTECTORS

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Int J Radiat Oncol Biol Phys; 10(9):1581-4 1984

Analogous to certain radiosensitizers which are too hydrophilic to enter tumor cells, certain radioprotectors, because of their hydrophilicity, may also be hindered from entering tumor cells and thus protect only normal tissues. In testing this hypothesis, we utilized thin layer chromatography as convenient means to measure radioprotector hydrophilicity. Dose reduction factors (DRF's) for hematopoietic radioprotection were determined in BALB/c mice given half maximum tolerated doses (MTD/2) of 11 radioprotectors 30 min prior to graded doses of gamma rays. DRF's for tumor protection were determined in MCa-11 tumor-bearing mice using a regrowth delay assay. Differential radioprotection was found to be significantly correlated ($r = 0.86$) with hydrophilicity. Thus, radioprotector hydrophilicity appears to be a significant factor in the differential radioprotection observed and should be useful in designing or selecting better differential radioprotectors.

251. FACTORS INFLUENCING THE OXIDATION OF CYSTEAMINE AND OTHER THIOLS: IMPLICATIONS FOR HYPERTHERMIC SENSITIZATION AND RADIATION PROTECTION

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Division of Radiation Biology, Case Western Reserve University, Cleveland, Ohio.

Radiat Res; 100(2):298-312 1984

Some of the factors influencing the oxygen uptake and peroxide formation for cysteamine (MEA) and other thiols in serum-supplemented modified McCoy's 5A, a well-known medium used to cultivate a variety of cells in vitro, have been studied. The oxidation of MEA and cysteine in modified McCoy's 5A has been compared with that in Ham's F-12, MEM, and phosphate-buffered saline. All of the growth media were supplemented with 10% calf serum and 5% fetal calf serum. The rate of oxygen uptake for all of the studied thiols was greatest in McCoy's 5A. The data indicate that this medium may contain more copper than the other preparations. MEA and cysteine were found to be more effective at 0.4 mM at producing peroxide than dithiothreitol (DTT). N-acetylcysteine was the least reactive. The ability to produce peroxide is dependent upon the temperature, the concentration of thiol, the presence of copper ions, and pH of the medium. MEA and other thiol oxidation is inhibited by the copper chelator diethyldithiocarbamate. Catalase also reduces the oxygen uptake for all thiols. This inhibition involves the recycling of peroxide to oxygen. Superoxide dismutase (SOD) was found to stimulate the oxygen uptake in the case of MEA and cysteine, but had little or no effect with DTT and glutathione. The combined presence of SOD and catalase resulted in less inhibition of oxygen uptake than that obtained by catalase alone. Alkaline pH was found to enhance the oxidation of cysteine and MEA. An important observation was the inhibition of MEA oxidation at 0 degrees C and the stimulation at 42 degrees C. The results indicate that many problems may arise when thiols are added to various media. A major consideration is concerned with the production of peroxide, superoxide, and reduced trace metal intermediates. The presence of these intermediates may result in the production of hydroxyl radical intermediates as well as the eventual oxygen depletion from the medium. Oxygen

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depletion may alter the results of radiation sterilization and carcinogen activation. Radical production will cause cell damage that is temperature dependent. Therefore, careful consideration must be given to changes in oxygen tension when thiols are added to cells growing in complicated growth medium to protect against either chemical or radiation damage.

252. IN VIVO MONITORING OF THE RADIATION PROTECTOR WR-2721 IN MICE USING 31P NMR SPECTROSCOPY (MEETING ABSTRACT)

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Proc Annu Meet Am Assoc Cancer Res; 26:360 1985

We have found that phosphorus-31 nuclear magnetic resonance (31P NMR) spectroscopy is suitable for monitoring the presence of WR-2721 (S-2-(3-aminopropylamino) ethylphosphorothioic acid) both in vitro and in vivo. The NMR signal due to the phosphorus nucleus of the thiophosphate group in WR-2721 occurs in a region of the spectrum where there is no interference from the phosphorus compounds normally found in tissues and tumor. WR-2721 was administered at a dose of 400 mg/kg to a Balb/c mouse by intramuscular injection into the thigh. The muscle was monitored at the point of injection using a surface coil to obtain the 31P NMR spectra before and at 20, 40 and 80 min after drug injection. Similarly, WR-2721 was administered at a dose of 400 mg/kg intratumorally to a Balb/c mouse bearing an EMT6 tumor in the hind leg. NMR spectra of the tumor was recorded before and at 20, 40 and 80 min post injection. The thiophosphate signal was clearly seen in all spectra obtained after administration of WR-2721. This signal which was most intense in the spectra acquired at 20 min after drug injection, decreased progressively in the spectra acquired at later times. The rate of loss of WR-2721 signal was markedly faster from the well vascularized muscle compared to that from the poorly vascularized tumor. In the case of spectra from the tumor, the loss of WR-2721 signal was accompanied by a concomitant increase in inorganic phosphate signal. Such an increase in inorganic phosphate signal was not seen in the spectra from muscle. These results suggest that significant dephosphorylation of WR-2721 can occur in the EMT6 tumor. In vivo 31P NMR spectroscopy provides a noninvasive method for studying the pharmacokinetics of WR-2721.

253. TOXICITY AND DISTRIBUTION OF [S-35]-WR2721 IN RAT BRAIN AND CEREBROSPINAL FLUID FOLLOWING INTRAVENTRICULAR INJECTION (MEETING ABSTRACT)

Spence AM, Krohn KA, Anderson KW, Mahler PA, Grunbaum Z
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Thirty-Second Annual Meeting of the Radiation Research Society, March 25-29, 1984, Orlando, Florida, p. 36, 1984.

To begin to determine whether WR2721 provides radioprotection in normal brain and spinal cord, acute toxicity and biodistribution studies were performed in F-344 rats. Unlabeled WR2721 was injected stereotaxically into the right lateral ventricle in 5 to 10 ul vol in graduated doses from 2.7 x 10(-2) ug to 1.23 mg. The toxic effects were ataxia, somnolence, lethargy, or death. The dose found to produce only mild effects in 100% of the animals was between 100 and 400 ug. Tissue concentrations of [S-35]-WR2721 were measured at time points between 45 and 110 min after injections of 100 to 200 ug/rat. Assuming no biotransformation of the compound and back-correcting results to a uniform 100 ug dose, we found the highest levels of 20 to 26 ug/g of tissue in the cerebellum, medulla, cervical spinal cord, and right hemisphere injection tract. Other cerebral hemisphere regions contained 3.5 ug/g or less. CSF contained 7.2 +/- 6.2 (SD, n=5) mg/ml. HPLC of the CSF showed that one-half of the activity was WR2721, and the remainder was divided between WR1065 and unsymmetrical disulfides.

254. EFFECTS OF PHYSIOLOGICAL SULFHYDRYL-REACTIVE COMPOUNDS ON MICROTUBULE ASSEMBLY AND COLCHICINE BINDING (MEETING ABSTRACT)

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J Cell Biol; 99(4):39a 1984

A variety of non-physiological sulfhydryl-reactive reagents are known to inhibit microtubule assembly, but little is known about the possible interactions of physiological reagents with tubulin. We have worked with two such compounds, cystamine (CYST) and reduced glutathione (GSH). CYST inhibits microtubule assembly in a dose-dependent manner. At higher concentrations CYST induces formation of abnormal tubulin polymers from microtubule proteins as well as pure tubulin. This polymerization is inhibited by GSH, DTT, cysteamine and oxidized glutathione (GSSG). GSH also induces formation of tubulin aggregates at lower ionic strength. Aggregate formation induced by CYST and GSH is inhibited at high ionic strength. Both CYST and GSH inhibited colchicine (COL) binding to tubulin under conditions where aggregate formation was favored. Incubation of tubulin with [35S]-CYST revealed the modification of 4-5 sulfhydryl (SH) groups per mole of tubulin in the polymer and of 2 SH groups in unpolymerized tubulin. Incorporation of [35S]-CYST is inhibited by GSH, GSSG, DDT, cysteamine and ethylene-bis(iodoacetamide) but can occur both at 0 C and at 37 C. COL and vinblastine inhibit CYST incorporation whereas podophyllotoxin and maytansine have no effect. Incorporation of CYST into a complex of tubulin and [3H]COL resulted in the release of COL at 37 C but had little effect at 0 C. These results suggest that CYST has a complex interaction with tubulin, perhaps in a region of the tubulin molecule involved in assembly and colchicine binding.

255. RADIOPROTECTIVE AND HEMODYNAMIC EFFECTS OF WR-2721 AND CYSTAMINE IN RATS: TIME COURSE STUDIES

Kuna P, Volenec K, Vodicka I, Dostal M
Purkyne Medical Research Institute, Hradec Kralove, Czechoslovakia.
Neoplasma; 30(3):349-57 1983

In experiments on rats radioprotective dose of WR-2721 (200 mg/kg) and cystamine (50 mg/kg) exhibited significant protective effects against radiation death during the first hour after their i. m. administration. Gamma rays were delivered with the dose rate of 0.35-0.31 Gy/min in gradually increased doses for the calculation of LD values and relative efficacy of the whole body irradiation. WR-2721 afforded protection with the highest dose reduction factor (DRF) of 1.51, while the best DRF value after cystamine was 1.36. No protection was found when the interval between injection of both protectors and the beginning of irradiation was longer than 60 min. WR-2721 as well as cystamine induced in pentobarbital anesthetized rats significant depression of cardiac output, hypotension and bradycardia immediately after their i. m. injections. The signs of depression of the hemodynamics persisted throughout the 4-hour observation period. Our results indicate that the hemodynamic effects of WR-2721 and of cystamine are not important for their radioprotective actions in rats.

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256. ROLE OF ENDOGENOUS SUBSTANCES IN INCREASED RADIORESISTANCE. 13. EFFECT OF VARIOUS RADIOPROTECTORS ON LIPID PEROXIDATION

Gurevich AV, Platonov AG, Deev LI, Kudriashov IuB
Faculty Biology, M. V. Lomonosov State Univ., Moscow, USSR
Radiobiologiia; 22(4):548-551 1982

Effects of the radioprotectors serotonin (ST) and aminoethylisothiuronium (AET) on lipid peroxidation were studied in male random-bred rats. The animals received single ip injections of ST at 60 mg/kg or AET at 250 mg/kg. Analysis of contents of lipid hydroperoxide in different tissues of the ST-tested animals showed that the ST decreased the contents of hydroperoxide in the liver and small intestine mucosa, while the AET decreased the content of hydroperoxides only in the liver. Results of in vitro incubation of liver microsomes with the radioprotectors showed that the ST was more effective t han the AET in inhibiting lipid peroxidation. (16 Refs)

257. GLUTATHIONE - AN ESSENTIAL COMPONENT OF RADIO-MODIFYING ACTION OF SEROTONIN

Konstantinova MM, Minin AA, Dontsova GV, Panaeva SV
Radiobiologiia; 23(6):811-3 1983

5-HT applied prior to, immediately or 5 min after irradiation decreased equally the radiation damage to Ehrlich ascite tumor cells. A decrease in the endogenous glutathione content by N-ethylmaleimide (NEM) led to reduced the 5-HT radio-modifying effect. Its radio-modifying effect decreased irrespective of whether NEM was applied prior to or after irradiation.

258. THE TIME COURSE OF RADIOPROTECTION BY WR 2721 IN MOUSE SKIN

Travis EL, De Luca AM, Fowler JF, Padikal TN
Radiation Oncology Branch, NCI, NIH, Building 10, Room B3B38, Bethesda, MD, 20205
Int J Radiat Oncol Biol Phys; 8(5):843-450 1982

The time course of radioprotection was studied using a series of intervals from 5-60 min after iv or ip injection of S-2-(3-aminopropyl-amino) ethyl phosphorothioate (WR 2721) in male albino BALB/c/An mice. The radiobiological endpoint was the acute skin reaction in the foot of white mice. Electrons (7 megaelectronvolt) were used because a high dose was required to keep the irradiation times short. A clear decrease in temperature of the mice was observed between 30 min and 3 hr after either ip or iv injection of 400 mg/kg WR 2721. Significant radioprotection was obtained at the 5-min interval (dose modifying factor; DMF 1.3), but it was much smaller than that obtained at the 30-, 45-, or 60-min intervals (DMF of 1.7-2.2). Data indicated that the amount of skin protection was generally constant over the single dose range of electrons used, although the DMF appeared to decrease after the higher dose of electrons. Consistently less protection was observed 15 min after drug administration than at 30 min, although the difference was not significant in all the experiments. More protection was observed at all times after iv injection than after ip injection of WR 2721. When WR 2721 was given ip 30 min prior to irradiation, the extent of protection in oxygen increased with increasing x-ray dose, while over the same dose range in air protection decreased with increasing dose. Data suggested that high concentration of oxygen diminish protection by WR 2721. (23 Refs)

259. IN VITRO STUDIES ON THE ABSORPTION OF WR-2721 BY TUMORS AND NORMAL TISSUES

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Int J Radiat Oncol Biol Phys; 8(3/4):523-526 1982

Single-cell system models were studied for possible use in studies of the absorption of the radioprotectant WR-2721. Single-cell suspensions (SCS) were made from normal liver and kidney tissues of BALB/c mice and Fisher 344 rats by means of mechanical dissociation methods. SCS of tumor tissues were prepared by mechanical and, in some cases, enzymatic dissociation. Human fibroblast cultures were prepared from diploid CC105 cells and from HeLa cells. Cultures were exposed to 1 or 2 uM WR-2721 or sodium thiosulfate for 0.5 hr before and during irradiation with 137Cs gamma-rays. Cultures were then incubated for 2 wk. Radiation survival was measured as colony-forming ability. SCS of normal rat and mouse tissues prepared by mechanical means were suitable for studying absorption of WR-2721. These cultures concentrated the drug against a gradient; absorption was reduced at 4 C, indicating that the cells concentrated WR-2721 by metabolic action. Rat RBC absorbed WR-2721 only passively. Bone marrow, which responded strongly to WR-2721 in vivo, responded poorly in vitro. Poor absorption was due to contamination of cell cultures with RBC and lipid. Use of tumor cell SCS was limited by low cell yields, contamination by non-tumor cells of host origin, and possible disruption of cell membranes. WR-2721 protected monolayer cultures of human fibroblasts only slightly from radiation damage and not at all from DNA strand breaks. The tumor and human fibroblast models studied are evidently not suitable for studies of the absorption of WR-2721. (12 Refs)

260. CIRCUMVENTION OF THE TUMOR MEMBRANE BARRIER TO WR-2721 ABSORPTION BY REDUCTION OF DRUG HYDROPHILICITY

Yuhas JM, Davis ME, Glover D, Brown DQ, Ritter M
Dept. Radiation Therapy, Univ. Pennsylvania, Philadelphia, PA, 19104
Int J Radiat Oncol Biol Phys; 8(3/4):519-522 1982

The relationships between structural and biophysical characteristics of the radioprotectant aminopropylaminoethylphosphorothioate (WR-2721) and the limited ability of WR-2721 to cross the cell membrane of tumor cells was studied. Multicellular tumor spheroids (MTS) of NB-100 human neuroblastoma tumor cells and rat RBC were used for absorption studies. Cell cultures were exposed in vitro to labeled doses of WR-2721, dephosphorylation products of WR-2721, B-mercaptoethylamine (MEA), cysteine or sodium thiosulfate (STF). All drugs were administered at initial concentrations of 10 uM. Octanol:water partition coefficients (PE) were calculated for all drugs. Addition of polyamines to WR-2721 did not inhibit absorption of the drug by normal cells or stimulate absorption by tumor cells. The PE of WR-2721 was between 0.00065 and 0.00045, indicating that the drug is very hydrophilic. Two dephosphorylation products of WR-2721, designated RSSR and RSH, had PE of 0.004 and 0.002, respectively, indicating that these two compounds were less hydrophilic. A mixture of RSSR and RSH showed 2.6x greater absorption by tumor cells at 37 C and 2x greater absorption at 4 C than did WR-2721. MEA and cysteine, both of which had PE greater than 0.001, were readily absorbed by normal and tumor cells. STF, which is very hydrophilic, was not readily absorbed by normal or tumor cells. Data indicate that hydr ophilicity affects the absorption of drugs by cells, and that differences in absorption by normal and tumor cells

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allows selective absorption of WR-2721 by normal cells. (9 Refs)

261. POSSIBLE ASSOCIATION OF RADIOPROTECTIVE AND CHEMOPROTECTIVE AMINOPHOSPHOROTHIOATE DRUG ACTIVITY WITH POLYAMINE OXIDASE SUSCEPTIBILITY

Gaugas JM

International Immunotechnology Corp., 4904 West Cypress St., Tampa, FL, 33607

JNCI; 69(2):329-332 1982

The aminophosphorothioate drug S-2-(3-aminopropylamino)ethylphosphorothioate (WR-2721) is both radioprotective and chemoprotective, with potential clinical use in cancer therapies. These distinct properties may be associated with its catabolism by polyamine oxidase (EC 1.4.3.4), which is found in varying amounts in different body tissues. Unfortunately, the metabolites is probably a cytotoxic aldehyde, but it should be detoxified in vivo following adduction with tissue sulfhydryls. Whether conversion and adduction benefit or hinder pharmacologic activity is not known, inasmuch as aldehydes may reduce oxygen-dependent free radicals generated by irradiation of tissues. S-2-(3-aminopropylamino)propylphosphorothioate was similarly a substrate for polyamine oxidase, and the product was cytotoxic. Other aminophosphorothioates [S-2-(4-aminobutaneamino)ethylphosphorothioate, S-2-(5-aminopentylamino)ethylphosphorothioate, and S-2-(4-aminobutaneamino)propylphosphorothioate] were poor substrates and less radioprotective. (Author abstract) (20 Refs)

262. PROTECTIVE DRUGS IN CANCER THERAPY: OPTIMAL CLINICAL TESTING AND FUTURE DIRECTIONS

Yuhas JM

Dept. Radiation Therapy, Univ. Pennsylvania, Philadelphia, PA, 19104

Int J Radiat Oncol Biol Phys; 8(3/4):513-517 1982

The role of aminopropylaminoethyl-phosphorothioic acid (WR-2721) in selective protection in vivo, in vitro and biophysical studies, and problems and future directions in clinical testing are discussed. Absorption of C-14 labeled WR-2721 by 1 mm cubes of normal tissues and of selected tumors is presented. Sensitivity to change in pH as a function of pH for WR-2721 and selected radioprotective drugs is illustrated. Given the fact that perent WR-2721 does not penetrate tumor cells, while its dephosphorylated analogues do, indicates that caution must be exerted in using the drug both in the laboratory and clinic. (8 Refs)

263. ROLE OF ENDOGENOUS SUBSTANCES IN CREATION OF THE POOL OF INCREASED RADIORESISTANCE. COMMUNICATION 16. EFFECT OF VARIOUS AET DERIVATIVES IN THE ENDOGENOUS RADIORESISTANCE

Goncharenko EN, Stsev SV, Graevskaia EE

Faculty Biology, M. V. Lomonosov State Univ., Moscow, USSR

Radiobiologiia; 22(2):252-255 1982

The mechanism of radioprotective effect of 8-aminoethylisothiuronium (AET) derivatives was studied in male albino mice. Administration of adeturon and 2-amino-4-iminothiazoline produced a marked decre ase of the level of endogenous radiosensitizers (hydroperoxides of higher unsaturated fatty acids) and the increase of the level of endogenous radioprotectors (serotonin and histamine) in the spleen, small intestine, liver, and stomach of irradiated animals. (8 Refs)

264. REDUCED GLUTATHIONE CONCENTRATION AND GLUTATHIONE REDUCTASE ACTIVITY IN VARIOUS TISSUE AFTER THE ADMINISTRATION OF SOME RADIOPROTECTIVE AGENTS

Pulpanova J, Kovarova H, Ledvina M

Institut fur Medizinische Biochemie, Medizinische Fakultat der Karls-Universitat, 50038 Hradec Kralove, Czechoslovakia

Radiobiol Radiother (Berl); 23(1):42-49 1982

Changes in reduced glutathione (GSH) and in the activity of glutathione reductase (AGR) were evaluated in tissues (liver, kidney, and spleen) of rats after ip administration of cystamine (CY: 50 mg of base/kg), mexamine (ME: 10 mg of base/kg), or both (20 mg and 10 mg of base/kg). The GSH increased in all tissue after the CY reached a max at 20-60 min. CY and ME max was reached sooner, and ME alone did not show a significant effect. The AGR was considerably reduced in liver and in kidney, and only slightly in the spleen after administration of CY, and CY with ME. ME alone had practically no effect. (21 Refs)

265. RADIOPROTECTION BY THIAZOLIDINES AT THE CELLULAR LEVEL

Vos O, Budke L, Fatome M, Van Hooidonk C

Medical Biological Lab., TNO, 139 Lange Kleiweg, P. O. Box 45, 2280 AA Rijswijk ZH, The Netherlands

Int J Radiat Biol; 39(3):291-296 1981

Radioprotection by a number of thiazolidine derivatives was studied in vitro. Reproductive integrity of single cells was used as a parameter for survival after irradiation. Thiazolidine itself did not protect when dissolved in culture medium, but a good protective activity was found when it was dissolved in rat blood. Rat blood improved also the radioprotective activity of most other thiazolidine derivatives. The best protection was obtained with thiazolidines in which the carbon at the 2 position was substituted by germanium. No correlation was evident between the degree of protection and release of a free SH group by hydrolysis of the thiazolidine ring. The results support a previous suggestion by Terol, Fernandez, Robbe, Chapat, Granger an Sentenac-Rovmanov that the thiazolidines proper and not their hydrolysis products are responsible for radioprotection. (Author abstract) (13 Refs)

266. DISTRIBUTION OF 35S IN MICE AFTER ORAL ADMINISTRATION OF ALPHA-DITHIOACETAMIDINIUM CHLORIDE: AN AUTORADIOGRAPHIC INVESTIGATION

Dencker L, Rebbinder C, Ronnback C, Carfagnini JC, Stridsberg B

(c/o Rebbinder) Dept. Pathology, Swedish Univ. Agricultural Sciences, S-750 07 Uppsala, Sweden

Acta Radiol Oncol Radiat Phys Biol; 20(4):273-277 1981

The distribution of 35S in mice has been investigated by whole-body autoradiography after oral administration of the 35S labeled S-75 (2,2'-Dithiobis *N-k(1-adamantyl)-methyll-acetamidine* dihydr ochloride). The substance was rapidly absorbed, and the highest concentration occurred in the liver and kidneys. During the highest radiation protective activity (after about 45 min) a substantial concentration was found in the red pulp of the spleen. This supports previous findings that S-75 has its most marked protective effect on the splenic hemopoiesis. Previously, it was shown that cysteamine is more evenly distributed in the body than S-75, which is in agreement with its more generalized protective effect than S-75. (Author abstract) (14 Refs)

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267. RADIOPROTECTIVE AND HEMODYNAMIC ACTION OF CYSTAMINE GIVEN INTRAMUSCULARLY IN RATS

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Purkyne Medical Res. Inst., 50260 Hradec Kralove, Czechoslovakia

Radiobiol Radiother (Berl); 22(6):793-800 1981

The radioprotective and hemodynamic effectiveness of cystamine administered im to adult male and female Wistar SPF rats was studied. Small intestine cellularity and dry spleen mass showed a drop on days 2 and 4 following whole body gamma irradiation (10 Gray) in cystamine-protected rats (CPR) and controls; CPR recovered. Values of mean lethal doses for the 30-day interval following whole body gamma irradiation which indicate injury to the hemopoietic system are presented. Im and ip administration of 50 or 60 mg cystamine/kg 10-20 min before irradiation afforded significant protection. Hemodynamic examination was conducted in three groups of rats: Group I received saline im, Group II cystamine im, and Group III cystamine ip. A drop in arterial pressure induced by ip cystamine injection was moderated by im injection of the same dose of cystamine. Post-cystamine bradycardia and decrease in cardiac output showed the same reaction. Significant depression of blood flow through spleen, salivary glands, and skin was observed after ip cystamine application. Significant elevation of blood flow in the wall of small intestine was observed after cystamine application. (24 Refs)

268. RADIOPROTECTIVE EFFECT OF 5-HYDROXYTRYPTOPHAN AND 5-HYDROXYTRYPTAMINE IN MASTOCYTOMA CELLS AGAINST IRRADIATION IN VITRO

Sato T, Nakamura W

Dept. Experimental Radiology, Aichi Cancer Center Res. Inst., Chikusa-ku, Nagoya 464, Japan

Nippon Igaku Hoshasen Gakkai Zasshi; 41(9):868-872 1981

The radioprotective effect in vitro of 5-hydroxytryptophan (HTP) and 5-hydroxytryptamine (5-HT) was studied with cultured mastocytoma cells of cell line P815A. Pre-incubation of the cells for 30 min in a 5-HTP-containing medium resulted in a great accumulation of 5-HTP which reached the level 80 times higher than in control. In these cells, no appreciable amount of 5-HT was detected, and their radiosensitivity remained unchanged. Whereas, the pre-incubation of the cells for 30 min in a 5-HT-containing medium induced a considerable elevation of the 5-HT content concomitantly with an increase in the radioresistance of cells. Thus, it was clearly evidenced that the 5-HTP per se in cells was ina ctive to modify the radiosensitivity of the cells, although it acted as a potent radioprotector in the cells which had the capacity to convert it into 5-HT. By chemical analysis, it was indicated that the principal amount of 5-HTP in P815A cells and that of 5-HT in FMA cells was distributed in cytoplasm. (Author abstract) (11 Refs)

269. ROLE OF BETA-ADRENERGIC RECEPTORS IN THE RADIOPROTECTIVE EFFECT OF ISOPROTERENOL

Granvskii EI, Sobolev AS, Smirnova IB, Chirkov IuIu, Dontsova GV, Granvskaia EE

N. K. Kol'tsov Inst. Biology of Development, Moscow, USSR

Radiobiologiia; 21(5):688-693 1981

Administration of isoproterenol (IP) increased the survival of (CBA x C57BL)F1 mice irradiated with 900 rads and increased the radioresistance of isolated bone marrow cells. The beta-adrenergic receptor antagonist propranolol inhibited the radioprotective effect of the IP. These findings were indicative of a beta-adrenergic mechanism for the radioprotective effect of IP. (11 Refs)

270. ACTIVE VERSUS PASSIVE ABSORPTION KINETICS AS THE BASIS FOR SELECTIVE PROTECTION OF NORMAL TISSUES BY S-2-(3-AMINOPROPYLAMINO)-ETHYLPHOSPHOROTHIOIC ACID

Yuhas JM

Cancer Res. Treatment Center, Univ. New Mexico, Albuquerque, NM, 87131

Cancer Res; 40(5):1519-1524 1980

Through an in vivo and in vitro analysis of the absorption kinetics of S-2-(3-aminopropylamino)ethylphosphorothioic acid (WR-2721) in the normal tissues and solid tumors of mice, rats, and rabbits, it has been demonstrated that normal tissues actively concentrate WR-2721 against a concentration gradient, whereas solid tumors passively absorb it, or, if active concentration of WR-2721 is present in tumors, it operates at a far reduced rate relative to normal tissues. These observations can account for the ability of WR-2721 to selectively protect normal tissues against both radiation and alkylating agent injury. (Author abstract) (12 Refs)

271. EFFECT OF CYSTEINE ON MEMBRANES OF NORMAL AND GAMMA IRRADIATED EAC CELLS

Polivoda BI

Res. Inst. Medical Radiology, Obninsk, USSR

Radiobiologiia; 20(1):117-120 1980

The evaluation of the radioprotector effect of cysteine on some biophysical properties of normal and irradiated cells of Ehrlich ascites carcinoma (EAC) is presented. A 7-8-day cultures cells were incubated with cysteine (0-500 mg/liter) for 10 min and then irradiated with Co60 gamma rays (20 R/sec, total dose 5,000 R). Parameters of cells were measured 4 hr after irradiation. Analysis of kinetic characteristics of cell swelling showed that cysteine had a marked effect on the stability of cell membranes; at concentrations of 100 mg/liter cysteine blocked the destabilizing effect of radiation, providing the radioprotective effect, while at 200-500 mg/liter cysteine per se had such a destabilizing effect on cell membranes that irradiation did not change the characteristics of cell swelling. (12 Refs)

272. DEPHOSPHORYLATION OF WR-2721 TO WR-1065 IN VITRO AND EFFECT OF WR-1065 AND MISONIDAZOLE IN COMBINATION IN IRRADIATED CELLS

Purdie JW

Defence Res. Establishment Ottawa, Dept. Natl. Defence, Ottawa, Canada

Radiation Sensitizers: Their Use in the Clinical Management of Cancer. Brady LW, ed. New York, Masson Publishing USA, Inc., Cancer Management, Vol. 5, 321 pp., 1980.

Production of free thiol in vitro was measured to determine if slow growth of protection with WR-2721 results from slow hydrolysis in the presence of cells. Combination of the radioprotector WR-1065 and misonidazole was tested in human kidney T-cells. The relationship between WR-2721 and WR-1065 was studied; dose reduction factors were measured in vitro after drug treatment 30 min prior to irradiation. Results indicated that free thiol is slowly released from WR-2721 in the presence of cultured cells. WR-1065, the active thiol from WR-2721, protected cells under oxic and anoxic conditions even in the presence of equimolar concentration of misonidazole. (12 Refs)

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273. THE CONCENTRATIONS OF SH-GROUPS IN SOME RADIOSENSITIVE TISSUES AFTER THE ADMINISTRATION OF RADIOPROTECTORS IN RATS

Stuklasova A, Krizala J, Ledvina M
Dept. Biochemistry, Faculty Medicine, Charles Univ., 50038 Hradec Kralove, Czechoslovakia
Strahlentherapie; 156(3):205-209 1980

The changes in the concentrations of total, nonprotein and protein SH-groups were spectrophotometrically determined in the small intestine and bone marrow of the rats 10, 20, 30 and 60 min after the administration of protective doses of cystamine (50 mg/kg), mexamine (10 mg/kg) or of a mixture of cystamine with mexamine (20 + 10 mg/kg). Cystamine caused an increase in the concentration of mainly nonprotein thiols, whereas the mexamine administration increased the protein SH-groups (mainly between the 20-30 min after treatment). The radioprotective mixture led to the most pronounced increase at the 10 min interval. This increase at the 10 and 20 min intervals was more pronounced (or identical) than after cystamine or mexamine administered as a single agent. If the SH-concentration should correspond to the degree of radioprotection, then the phenomenon observed would indicate the usefulness of the mixture administered. (Author abstract) (14 Refs)

274. POSSIBILITY OF MODIFYING THE DISTRIBUTION OF ORALLY ADMINISTERED 35S-APAETP USING OTHER RADIOPROTECTORS

Suvegin EV, Solovev InA, Belavina LP, Zherebchenko PG
No affiliation given
Radiobiologiia; 20(3):438-442 1980

The effect of radioprotectors, S-ethylisothiuronium and euspiran, on the distribution of S35-aminopropylaminoethylthiophosphate (S35-APAETP) was studied in CBWA mice. Animals were subjected to po administration of S35-APAETP (270 mg/kg); 15 min later rats were given S-ethylisothiuronium or euspiran. It was found that S-ethylisothiuronium had almost no effect on S35-APAETP distribution in cases of ip or inhalation administration; intragastric administration of S-ethylisothiuronium decreased the accumulation of label in the blood but increased the amount in the stomach wall. Inhalation or ip administration of euspiran increased S35-APAETP level in the majority or organs including the spleen and bone marrow. (10 Refs)

275. EVALUATION OF RADIOPROTECTIVE EFFICACY OF SOME AMINOALKYLTHIOPHOSPHORUS DERIVATIVES. COMMUNICATION 2. ANALYSIS OF RADIOPROTECTIVE EFFICACY OF SODIUM S-(S-THIOETHYL-2-AMINO) THIOPHOSPHATE

Sverdlov AG, Grachev SA, Bondarev GN, Bogatyrev AV, Kikanorova NG, Timoshenko SI, Kalmykova GI, Krasotskaia GI
B. P. Konstantinov Inst. Nuclear Physics, Leningrad, USSR
Radiobiologiia; 20(1):75-79 1980

The radioprotective efficacy of sodium S-(s-thioethyl-2 amino) thiophosphate Thiocystaphos) was studied in randombred albino mice. Radioprotector was given ip (300 mg/kg) or po (1,000 mg/kg) prior to irradiation with x-rays (400-1,000 R) or neutrons (200-300 R). The most pronounced radioprotective effect was recorded for ip administration 15-60 min prior to irradiation, 55% survival, compared with 45% survival during administration 2 hr prior to irradiation and 30% survival for the administration 3-4 hr before the irradiation). Thiocystaphos was slightly less effective during po administration, providing a 37.5% survival at irradiation with 700 R. (3 Refs)

276. A COMPARATIVE STUDY OF THE RADIOPROTECTIVE EFFECT OF CYSTEAMINE, WR-2721 AND WR-1065 IN CULTURED HUMAN CELLS

Purdie JW
Defense Res. Establishment Ottawa, Dept. Natl. Defense, Ottawa K1A 0Z4, Canada
Radiat Res; 77(2):303-311 1979

The mode of action, site of action, and transport rate of the radioprotective agents cysteamine, S-2(3-aminopropylamino)-ethylphosphorothioic acid (WR-2721), and N-(2-mercaptoethyl)-1,3-diaminopropane (WR-1065) in cells derived from human kidney (T cells) were studied. The toxicity of the compounds was examined by exposing the cells to concentrations varying from 1 to 128 milliM (mM) for periods up to 3 hr. The cells did not respond to high concentrations of the compounds or long exposures to WR-1065 or WR-2721, but the surviving fraction declined rapidly after exposure to cysteamine for more than 30 min. The response of the cells to irradiation following treatment for 30 min with 4 mM of each compound was measured. Survival curves were constructed, and the following dose reduction factors (DRF) calculated: WR-2721, 1.3; cysteamine, 2.3; and WR-1065, 2.9. The DFR values were determined for the three drugs at concentrations of 4 and 10 mM for extended preirradiation treatment times. The cysteamine curves reached a plateau after 10 min and declined rapidly after 30-45 min; no difference in protective efficiency between the two concentrations was observed. Both the curves of WR-2721 rose slowly with time of exposure. The WR-1065 curve showed a rapid rise in DFR until a plateau was r eached at 60 min; the 10 mM WR-1065 curve rose rapidly with treatment time for 45 min and slowly from 45 to 120 min. Cysteamine enters the cell rapidly and provides the max amount of protection after 10 min. The rate-controlling step for WR-1065 activity could be transport into the cell or into the nucleus or penetration of critical targets (DNA). The slow build-up of protection from WR-2721 may be due to the slow hydrolysis of the free thiol. (14 Refs)

277. RADIOPROTECTIVE EFFECT OF 2-MERCAPTOPROPIONYLGLYCINE ON THE INTESTINAL CRYPT OF SWISS ALBINO MICE AFTER COBALT-60 IRRADIATION

Uma Devi P, Saini MR, Sabaran BR, Bhartiya HC
Radiation Biology Lab., Univ. Rajasthan, Jaipur-302004, India
Radiat Res; 80(1):214-220 1979

Male Swiss Albino mice, 6-8 wk of age, were divided into two groups of equal number: one was injected ip with 20 mg/kg 2-mercaptopropionylglycine (MPG), a synthetic sulfhydryl compound effective in radiation protection at doses below its toxic dose (2,100 mg/kg), the second group was given a distilled water injection and served as controls. Thirty min after injection the animals in both groups were exposed to a cobalt-60 source so as to receive a total of 1,000 R in 42 min. At 3, 6, 12, 24, and 72 hr, and 5, 7, 14 and 28 days after irradiation a minimum of three animals from each group were sacrified and the jejunum prepared for histological examination. Exposure to 1,000 R of gamma rays produced 25% mortality in the control group by 28 days, of which 20% occurred between 7 and 10 days. No mortality was observed in the protected group. Changes at 3, 6 and 12 hr after radiation were the same in both groups, but pycnotic nuclei were fewer in the treated animals at 3 hr. Mitosis was totally inhibited in controls up to 24 hr. The max number of pycnotic nuclei and cells occurred at 3 hr; the number decreased after that and was minimal at 14 days. Mitoses were max at this time. The number of pycnotic nuclei showed a second rise at 28 days along with a reduction of mitoses. Anaphase bridges and abortive divisions were observed. In

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treated animals, mitotic figures began to be seen at 12 hr and were normal at 24 hr. By 72 hr cells resumed division. The mitotic peak occurred on day 5 and the number of mitoses was double that of the controls. The crypts thereafter showed rapid recovery which was more or less complete by day 28. The cell population was similar to that of unirradiated animals. Anaphase bridges were absent in treated animals. It was concluded that MPG probably protects DNA strands, and may do so by producing a long-lasting release of sulfhydryl compounds from proteins. (16 Refs)

278. **PREDICTION OF THE EFFECTIVE RADIOPROTECTIVE DOSE OF WR-2721 IN HUMANS THROUGH AN INTERSPECIES TISSUE DISTRIBUTION STUDY.**

Washburn LC, Rafter JJ, Hayes RL, Yuhas JM
Medical Health Sciences Div., Oak Ridge Associated Universities, Oak Ridge, TN 37830
Radiat Res; 66(1):100-105 1976

Tissue distribution of S-2-(3- aminopropylamino)- ethyl-phosphorothiotic acid (WR-2721) was studied at 15 and 30 min after iv injection of 35S-labeled WR-2731 in order to determine whether surface area or body wt was the more accurate parameter on which to base dosage. Male C57BL/6 mice, male Buffalo rats, female New Zealand white rabbits, and both sexes of laboratory grade beagle dogs were used. A nominal dose of 100 mg of WR2721 per kg was chosen. Identical tissue concentrations were not achieved either at 15 or 30 min after injection. Tissue distribution was not a strict function of either body wt or surface area, but rather fell intermediate to the predictions of those parameters. It is calculated that a dose of 20 mg/kg would be required to obtain a 50-80% increase in radioprotection in man, compared to 100 mg/kg in the mouse. (10 refs)

279. **DISTRIBUTION OF 35S-LABELED WR-2721 IN NORMAL AND MALIGNANT TISSUES OF THE MOUSE.**

Utley JF, Marlowe C, Wadell WJ
Dept. Radiation Medicine, Univ. Kentucky Medical Center, Lexington, KY 40506
Radiat Res: 68(2):284-291 1976

The distribution of S-2-(3-aminopropylamino)ethylphosphorothioic acid (WR-2721), labeled with S35, in malignant and normal tissues of the mouse is described. The drug was investigated in BALB/c mice bearing the mammary tumor, EMT-6; autoradiographs were made from sagittal sections at 60, 20, and 6 min following iv injection. In the skin, bone marrow, and intestinal mucosa, the radioactivity was high, rapid excretion of the drug by the kidneys was indicated by a high level in the kidney, decreasing rapidly over time. Over a 60-min period, the mammary tumor had a low concentration with only a small elevation. The concentration of WR-2721 correlated with the radioprotection produced by the drug. The salivary glands and the liver, two normal tissues demonstrating a high concentration of WR-2721, must be studied to determine whether there is some clinical importance. (14 refs)

280. **AN INTERSPECIES COMPARISON OF THE TISSUE DISTRIBUTION OF WR-2721, A RADIOPROTECTIVE DRUG**

Washburn LC, Rafter JJ, Hayes RL, Yuhas JM
Medical Health Sciences Div., Oak Ridge Associated Univ., Oak Ridge, TN 37830
Radiol Med Nucl; 3(10):28 1975

An interspecies comparison of the tissue distribution of S-2-[3-aminopropylamino]ethylphosphorothioic acid (WR-2721), a radioprotective drug, is presented. Investigations were carried out in normal dogs, rabbits, rats, and mice, 15 and 30 min following iv administration. The av WR-2721 tissue concentration for each species was normalized; a normalization factor for each mouse tissue was derived, and each factor was then multiplied by the observed concentration of the same tissue in the other species. The results indicated that the body wt and surface area exerted equal effects on the tissue co ncentration of WR-2721. It is concluded that the lower absolute doses of WR-2721 in humans, possibly as low as 20 mg/kg, may provide a radioprotective effect equivalent in that produced from 100 mg/kg in the mouse. (6 refs)

281. **DISTRIBUTION OF WR-2721 IN NORMAL AND MALIGNANT TISSUES OF MICE AND RATS BEARING SOLID TUMORS: DEPENDENCE ON TUMOR TYPE, DRUG DOSE AND SPECIES**

Washburn LC, Carlton JE, Hayes RL, Yuhas JM
Med. Div., Oak Ridge Assoc. Univs., Tenn.
Radiat Res; 59(2):475-483 1974

S-2-(3-Aminopropylamino)ethylphosphorothioic acid (WR-2721) preferentially protects normal, as opposed to malignant, tissues of tumor-bearing mice from radiation injury. The major factor responsible for this difference in response appears to be the relatively poor absorption of the drug by the tumor. Normal and tumor tissue concentrations of 35S-labeled WR-2721 were determined 30 minutes after injection of graded doses of the drug (1, 50, 100, or 300 mg/kg) into young male rats and mice bearing P-1798 lymphosarcomas, CA-755 adenocarcinomas (mice), RFT tumors, or Morris 7777 hepatomas (rats). Three of these solid tumors showed deficient drug absorption, although the Morris 7777 hepatoma absorbed WR-2721 as readily as the host's normal tissues. The relative concentration of the drug in normal and tumor tissued was independent of the injected dose between 50 and 300 mg/kg. The injection of tracer levels of WR-2721 (1 mg/kg) can be used to identify those tumors which exhibited deficient absorption, but not to quantitate the degree of deficiency. The relationship between the injected dose and tissue concentration, after correction for species differences in surface area, was species independent for the lungs, small intestine, and spleen, but species dependent for the kidney and liver. Thus, WR-2721 appears to be a promising agent for increasing the efficiency of solid tumor radiotherapy, provided that each tumor is considered individually.

282. **THE DISTRIBUTION OF CYSTOPHOS IN THE ORGANISM OF ANIMALS WITH TUMORS**

Airapetian GM, Anorova GA
Inst. Industr. Hygiene, Moscow
Med Radiol (Mosk); 12(3):58-65 1967

The distribution of sc admin. 35S- or 32Plabeled B-aminoethylthiophosphoric acid monosodium salt (Cystophos;C) was studied in rats with Sarcoma M-1 and C3H mice with spontaneous or inoc mammary adenocarcinoma. The max accumulation of 35S was seen after 1-2 hr in rats, the normal tissues showing a much greater concn of label (2.5-3 times higher) than the tumor; 32p accumulation was different because of active cleavage of the C molecule in the organism. Accumulation of 35S in mice was significantly more rapid than in rats and the max levels were about twice as high, but the difference between the tumor and the normal tissue was not as marked apparently because of the tumor's blood supply. Optimum radioprotective effects (according to survival data) were seen in mice admin. C 30 min before ir radiation and in rats treated 60-90 min before irradiation; this response coincided with max. C levels in the organs.

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V.

DRUG COMBINATIONS

A.

Radioprotectors and Radiosensitizers

283. COMBINED USE OF RADIOSENSITIZING AND PROTECTIVE AGENTS IN EXPERIMENTAL RADIOTHERAPY

Magdon E, Schroder E, Iarmonenko SP, Vygodskaia AL, Vinskaia NP

Med Radiol (Mosk); 29(12):29-32 1984

The appropriateness of the combined use of electron acceptor radiosensitizers: 4-nitroimidazole and metronidazole, and sulfhydryl protectors WR-2721 (gammaphos) and cysteamine was shown on the Chinese hamster cells V-79 and transplantable mouse tumors. The administration of the sensitizer 30-60 min and the protector 15-20 min before the irradiation of solid tumors weakens radiation reactions of the skin (metronidazole plus gammaphos) without weakening the effect of radiosensitization on transplantable animal tumors (metronidazole plus gammaphos or 4-nitroimidazole plus WR-2721).

284. COMBINED EFFECTS OF RADIOSENSITIZERS AND RADIOPROTECTORS ON CULTURED MAMMALIAN CELLS TO CO-60 GAMMA-RAYS

Antoku S, Hoshi M

J Radiat Res (Tokyo); 25(4):305-13 1984

Keywords (MeSH): Animal; Cell Survival; Cells, Cultured/*radiation effects; *Cobalt Radioisotopes; Cysteamine/pharmacodynamics; DNA, Neoplasm/*radiation effects; Glutathione/pharmacodynamics; Leukemia L5178/*pathology; Leukemia, Experimental/*pathology; Mice; Misonidazole/pharmacodynamics; Radiation-Protective Agents/*pharmacodynamics; Radiation-Sensitizing Agents/*pharmacodynamics; Thiourea/pharmacodynamics.

285. RADIOPROTECTION COMBINED WITH HYPOXIC SENSITIZATION DURING RADIOTHERAPY OF A SOLID MURINE TUMOR

Mendiondo OA, Grigsby PW, Beach JL

Department of Radiation Medicine, University of Kentucky Medical Center, Lexington.

Radiology; 148(1):291-3 1983

EMT6 tumors were transplanted intramuscularly in the right hind leg of female BALB/c mice and irradiated when they reached a diameter of 6-7 mm. Each mouse received an intraperitoneal injection of WR-2721, misonidazole, or both prior to irradiation, and the dose needed to control half of the tumors at 30 days (TCD50/30) was recorded. WR-2721 offered slight tumor protection, with a dose-modifying factor (DMF) of 1.04-1.15 for radioprotector doses of 150-500 mg/kg. Pretreatment with misonidazole at doses of 300-900 mg/kg yielded tumor sensitization with a DMF of 0.71-0.92. Pretreatment with both WR-2721 and misonidazole gave overall tumor sensitization with a DMF of 0.78-0.97. Possible combinations of sensitizers and protectors, while providing overall tumor sensitization, do not seem to improve the therapeutic ratio over what could be obtained from a sensitizer or protector alone.

286. INTERACTION OF RADIOSENSITIZERS AND WR-2721. I. MODIFICATION OF SKIN RADIOPROTECTION

Rojas A, Stewart FA, Denekamp J

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Br J Cancer; 45(5):684-693 1982

We have studied the radiomodifying action in mouse skin of WR-2721 and misonidazole (MISO) when used alone or in combination. The radioprotection with WR-2721 was drug-dose dependent and highly influenced by the O2 concentration at the time of irradiation. Significant sensitization was observed with MISO, especially in air-breathing mice. The combination of WR-2721 and MISO produced a radiation response intermediate between the resistant and sensitive responses to either drug alone. The precise degree of sensitivity was dependent on the relative doses of protector and sensitizer. We have also studied the interaction of both drugs in terms of drug-induced lethality, which showed a clear toxic interaction. The WR-2721 LD50 was reduced by a factor of 1.4 with only 200 mg/kg of MISO. We conclude that the combination of WR-2721 and MISO shows an interaction in terms of drug toxicity and radiation response, such that the radioprotection of skin is reduced or even abolished with low doses of MISO. (Author abstract) (43 Refs)

287. INTERACTION OF MISONIDAZOLE AND WR-2721-II. MODIFICATION OF TUMOUR RADIOSENSITIZATION

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Br J Cancer; 47(1):65-72 1983

Two types of mouse tumor have been used to study the radiomodifying actions of misonidazole (MISO) and WR-2721 when used alone and in combination with each other. Single dose studies were performed in both of the tumors and fractionated studies were performed on the anaplastic carcinoma, CA MT. Radioprotection with WR-2721 was seen in both tumors, being most marked at low x-ray doses. The protection was more obvious and the sensitization by MISO less in the fractionated experiment. The combination of MISO and WR-2721 gave an intermediate response compared with either drug used alone, resulting in some sensitization with single doses and an overall protection with repeated small doses. An interactive toxicity of the two drugs was also observed, suggesting an additive effect when assessed in terms of lethality. These studies indicate that the effects of both MISO and WR-2721 are dependent upon the oxygen status of the cells in the tumor, and that MISO can act in an oxygen-mimetic manner to modify the radioprotection observed with WR-2721. (Author abstract) (42 Refs)

288. EXPERIMENTAL RADIOTHERAPY WITH WR-2721 AND MISONIDAZOLE

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Int J Radiat Oncol Biol Phys; 8(3/4):527-530 1982

The protective effect of WR-2721, when used alone or in combination with misonidazole (MISO), was tested on mouse skin and on a variety of transplantable mouse tumors. The possible interactions of the sensitizer and protector were investigated, and the potential therapeutic advantage of some of the schedules were tested. WR-2721 could diminish the radiation responses of tumors and normal tissues in air breathing animals. The protection increased with increasing WR-2721 dose. The observed protection factor (PF) for skin was

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greater for mice breathing air than for those breathing oxygen. Some of the schedules were assessed in a way that determines whether the drug plus x-rays is better than the drug alone. For many of the single dose treatments using WR-2721, an increased tumor delay was observed relative to x-rays alone. Data obtained for skin and tumors when WR-2721 and MISO were combined in the same schedule are summarized. The addition of MISO reduced the protection observed with doses 200-500 mg/kg WR-2721, both in skin and tumors. Lethality experiments showed a marked interaction of the drugs in terms of the LD50. The LD50 for WR-2721 was reduced from 1,050 +-10 mg to 750 +-15 mg/kg when 200 mg/kg MISO was injected 15 min prior to WR-2721. The range of PF observed with WR-2721 in different normal tissues may result from variations in the endogenous sulfhydryl levels and the intracellular oxygen tension. These factors may also be important in determining the lower PF values generally observed in tumors, rather than a failure of the radioprotective drug to reach the critical cells. (11 Refs)

289. **COMBINED RADIOSENSITIZATION AND RADIOPROTECTION FOR ORAL CAVITY TUMORS: STUDY WITH AN ORAL CAVITY TUMOR CELL MODEL**

Grigsby P, Maruyama Y
Dept. Radiation Medicine, Univ. Kentucky Medical Center, 800 Rose St., Lexington, KY, 40536
Int J Radiat Oncol Biol Phys; 8(3/4):537-539 1982

Use of combined S-2-(3-aminopropylamino) ethylphosphorothioic acid (WR-2721), misonidazole (MIS), and single dose radiotherapy (0-3,500 centiGray) in treating an EMT 6/Ky tumor implanted in the buccal mucosa of female Balb/c mice was investigated. The tumor was injected as a cell suspension of 10(5) cells in 10 ul unilaterally into the buccal pouch. WR-2721 and/or MIS were injected ip 30 min prior to irradiation. Mean survival time (MST) and oral tumor death (OTD) were analyzed. In controls, MST ranged form 18.60-22.55 days for the OTD endpoint. With irradiation plus either WR-2721 or MIS, the MST increased above control level to a max of 29.08 days. MST increased with each incremental increase in radiation plus a given dose of WR-2721. At 1,500 centiGray, MST values for MIS at 700 or 300 mg/kg were significantly different from controls, while MST at 1,000 mg/kg was not. MST was not significantly different in any of the groups treated with irradistion, WR-2721 and MIS. The radioprotective ability of WR-2721 was increased when drug combinations of protection and sensitization were used at the max tolerated dose level, and combined with radiation using the ORD syndrome. The increase in MST was abolished when the radioprotector was combined with sensitizer, while the radioprotective ability of WR-2721 was retained. Direct competition at a common critical cellular binding site is postulated as the mechanism for these results. (5 Refs)

290. **MODIFICATION OF THE ORAL RADIATION DEATH SYNDROME WITH COMBINED WR-2721 AND MISONIDAZOLE**

Grigsby P, Maruyama Y
Radiation Medicine Dept., Univ. Kentucky Medical Sch., Lexington, KY, 40536
Br J Radiol; 54(647):969-972 1981

In order to investigate the combined use of radioprotective and radiosensitizing chemicals we have used WR-2721 and misonidazole to study their combined chemical toxicity and radiomodifying effects in our model using the oral radiation death (ORD) syndrome as the endpoint. Our data demonstrate that WR-2721 does protect against the ORD syndrome. Misonidazole does not sensitize the normal oral cavity to local irradiation. WR-2721 and misonidazole produce additive toxicity when injected simultaneously and the combination can provide an overall protective response to the ORD syndrome. We conclude that the combination may be potentially useful for the treatment of cancers of the oral cavity. (Author abstract) (12 Refs)

291. **COMBINED RADIATION-PROTECTIVE AND RADIATION-SENSITIZING AGENTS. II. RADIOSENSITIVITY OF HYPOXIC OR AEROBIC CHINESE HAMSTER FIBROBLASTS IN THE PRESENCE OF CYSTEAMINE AND MISONIDAZOLE: IMPLICATIONS FOR THE 'OXYGEN EFFECT' (WITH APPENDIX ON CALCULATION OF DOSE-MODIFYING FACTORS)**

Koch CJ, Howell RL
Cross Cancer Inst., 11560 University Ave., Edmonton, Alberta T6G 1Z2, Canada
Radiat Res; 87(2):265-283 1981

The radiation sensitivity of both hypoxic and aerobic cells exposed simultaneously to radiation-protector cysteamine (CS) and radiation-sensitizing agent misonidazole (MD) was studied in a culture of V79 Chinese hamster fibroblasts. MD at 2.5 milliM (mM) was found to sensitize hypoxic V79 cells to radiation by a factor of 2.1. Addition of CS to hypoxic cells containing MD provided protection against the radiosensitization by MD at concentrations as low as 0.1 mM. In aerobic cells, protection was achieved at CS concentration of greater than 1 mM of CS; at CS concentration of 30 mM, aerobic cells were as resistant as hypoxic cells without drug but still not as resistant as hypoxic cells with 30 mM of CS. These findings indicate that addition of CS cancels the benefit of MD and thus increases the differential response of hypoxic and aerobic cells. (48 Refs)

292. **HYPOXIC RADIOSENSITIZATION AND OXIC RADIOPROTECTION OF SINGLE CELL SUSPENSIONS AND MULTICELLULAR SPHEROIDS BY LOCAL ANESTHETICS**

Yau TM, Durand RE, Biaglow JE, Kim SC
Div. Radiation Biology, Dept. Radiology, Case Western Reserve Univ., Cleveland, OH
Radiation Sensitizers: Their Use in the Clinical Management of Cancer. Brady LW, ed. New York, Masson Publishing USA, Inc., Cancer Management, Vol. 5, 521 pp., 1980.

The response of multicellular spheroids of Chinese hamster lung V79 cells containing both euoxic and hypoxic fractions irradiated in the presence of a chemical which radioprotects euoxic cells and simultaneously radiosensitizes hypoxic cells was studied. The ability of local anesthetics to sensitize radiochemically but also to cause a certain degree of reoxygenation by inhibition of cellular respiration was tested; mechanism and site of action of these agents was examined. Lidocaine (LD) was found to have a radioprotective effect on irradiated oxic L5178Y lymphoma cells but a radiosensitizing effect on hypoxic cells. The effect was considered to be dose-modifying. LD, procaine (PC), and tetracaine (TC) effects with V79 spheroids were determined. At lower drug concentrations (where radioprotection or radiosensitization occurred minimally in single cell suspensions) radiosensitization of the hypoxic fraction of multicellular spheroids was observed. PC, LD, TC, and dibucaine inhibited V-79 cellular oxygen consumption. TC inhibited the electron transfer to ferricytochrome c + c1 but was not as effective as rotenone, and a longer time was required for the cytochromes to reach steady state. The effect of 4-nitroquinoline-N-oxide on the respiratory rate of TC-inhibited V79 cells indicated that inhibition of cellular oxidation by local anesthetics is probably mitochondrial. Local anesthetics appear to inhibit cellular

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oxygen consumption in a manner similar to rotenone or nitrotoluene, with possible action at the NADH-flavoprotein segment of the respiratory chain. (23 Refs)

293. CHEMORADIOPROTECTION OF THE RAT PAROTID GLAND BY COMBINED USE OF WR-2721 AND RO-07-0582

Sodicoff M, Conger AP, Pratt NE, Sinesi M, Trepper P
Dept. Anatomy, Temple Univ. Sch. Medicine, 3420 North Broad St., Phildelphia, Pa, 19140
Radiat Res; 80(?):348-353 1979

To test the combined in vivo effects of the oxygen-mimetic radiosensitizer drug, misonidazole (Ro-07-0582), and the radioprotective compound, WR-2721, female albino rats (180-250G) were anesthetized and subjected to x-irradiation of the right side of the head. Ro-07-0582 (200 mg/kg, ip) was injected 45 min prior to irradiation and WR-2721 (400 mg/kg, ip) was injected 15-20 min prior to irradiation. After overnight fasting, on preselected days after irradiation, both the irradiated and shielded parotid glands were removed and weighed. The within-animal wt ratio of the right (irradiated) to the left (shielded) gland was determined and used as a measure of the direct effect of irradiation on the gland. The observed wt ratio was converted to the 'corrected wt ratio' to allow for the fact that only 80% of gland wt can be lost from irradiation, due to the presence of radioresistant tissues. The irradiated and unirradiated experimental groups included (a) saline-injected control, (b) WR-2721 only, (c) Ro-07-0582 only, and (d) WR-2721 + Ro-07-0582. The results showed that at the same dose, t he amount of damage with WR-2721 was always less than for saline controls, with Ro-07-0582 it was about the same as the saline controls, and with Ro-07-0582 plus WR-2721 it was about the same as with WR-2721 alone; ie, the radioprotection afforded by WR-2721 alone was not diminished by combining it with Ro-07-0582. (19 Refs)

294. IN VITRO STUDIES ON THE RADIORESISTANCE OF OXIC AND HYPOXIC CELLS IN THE PRESENCE OF BOTH RADIOPROTECTIVE AND RADIOSENSITIZING DRUGS

Yuhas JM, Li AP
Cancer Res. and Treatment Center, Univ. New Mexico, Albuquerque, NM, 87131
Radiat Res; 75(3):563-572 1978

The effect of a combination of Ro-07-0582 (1-2-hydroxy-3-methoxypropyl-2-nitroimidazole), a hypoxic cell radiosensitizer, and cysteine, an oxic cell radioprotectant, on survival of K1 Chinese hamster ovary cells x-irradiated (800 rads) under oxic or hypoxic conditions was investigated. Cell survival was assayed as colony formation 7-9 days after irradiation. The drug concentrations that produced minimal toxic effects were 6 milliM Ro-07-0582 and 8 milliM cysteine. The ratio of survivors irradiated under hypoxic conditions (catalytic oxygen depletion) to survivors irradiated under oxic conditions was 93 in the absence of drugs, 6.1 in the presence of cysteine, 13.8 in the presence of Ro-07-0582, and 1.63 in the presence of both drugs. In the next experiment, cells were rendered hypoxic for periods of 15 min to 5 hr by gassing them with 95% N2 + 5% CO2. The survival of irradiated cells corrected for drug(s) and hypoxia toxicity divided by survival of irradiated oxic cells with no drugs was plotted against hr of hypoxia. This showed that a combination of drugs produced sensitization (relative to hypoxia alone) only slightly less efficiently than Ro-07-0582 at all hypoxic times greater than or equal to 1 hr, while it protected well-oxygenated cells nearly as effectively as cysteine alone. The combination of 6 milliM Ro-07-0582 and 8 milliM cysteine protects well-oxygenated cells from x-irradiation but sensitizes hypoxic ones. (16 Refs)

295. COMBINED USE OF RADIOPROTECTIVE AND RADIOSENSITIZING DRUGS IN EXPERIMENTAL RADIOTHERAPY

Yuhas JM, Yurconic M, Kligerman MM, West G, Peterson DF
Cancer Res. and Treatment Center, Dept. Radiology, Univ. New Mexico, Albuquerque, NM 87131
Radiat Res; 70(2):433-443 1977

The efficacy and toxicity of combining radioprotective and radiosensitizing drugs were studied in BALB/c mice bearing line 1 carcinoma. When 1-(2-nitro-1-imidazoyl)-3-methoxy-2-propanol (Ro-07-0582) was injected ip (290 mg/kg) 45 min before exposure to radiation at doses up to 6,000 rads and when S-2-(3-aminopropylamino) ethylphosphorothioic acid (WR-2721) was injected ip (400 mg/kg) 15 min before irradiation of tumor-bearing mice, the time required for the tumors to grow from 8 to 12 mm was significantly prolonged when both drugs were given in combination or when the radiosensitizer Ro-07-058 2 was given alone. The ED50 values for control mice, Ro-07-0582-treated mice, and mice receiving Ro-07-0582 plus WR-2721 were 3,290 +- 210, 2,100 +- 240, and 2,250 +- 251 rads, respectively. Ro-07-0582 at doses of up to 600 mg/kg did not alter the toxicity of WR-2721 (LD50 = 753 +- 16 mg/kg), and WR-2721 did not interfere with the ability of Ro-07-0582 to sensitize tumors in vivo. Moreover, Ro-07-0582 did not interfere with the ability of WR-2721 to protect mouse skin. (15 Refs)

B.

Other Combinations

296. INCREASED PROTECTIVE EFFECT OF CYSTAMINE AND MEXAMINE AGAINST RADIATION AFTER ACTIVATION OF THE HAEMOPOIESIS BY DEXTRAN SULPHATE IN MICE

Vacek A, Bartonickova A, Palyga GF, Zbukova NA
Institute of Biophysics, Czechoslovak Academy of Sciences, Brno.
Acta Radiol kOncol; 24(2):193-8 1985

The effect gained by activation of haemopoietic cell populations by a single injection of dextran sulphate (DS) on the protective effect of cystamine and mexamine administered in small doses was monitored in mice. On irradiation 24 hours after the injection of DS the number of endogenous spleen colonies increased following the administration of mexamine and cystamine, the number of haemopoietic stem cells surviving in the femur after irradiation increased, and recovery of the cellularity of irradiated bone marrow was accelerated. Both substances administered 24 hours after the injection of DS significantly reduced the lethal effects of gamma rays. The maximum values of the dose reduction factor, for combined radiation protection, reached 1.48 as regards decreased lethal effects and 1.6 as regards equieffective E-MSC exposure.

297. POTENTIATION OF NITROGEN MUSTARD CYTOTOXICITY TO LEUKEMIA CELLS BY THIOLS ADMINISTERED IN VIVO (MEETING ABSTRACT)

Valeriote F, Grates HE
Div. of Medical Oncology, Dept. of Medicine, Wayne State Univ., Detroit, MI 48201
Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 2-21, 1985.

It has been previously demonstrated that the cytotoxicity of nitrogen mustard (HN2) to an AKR leukemia can be significantly potentiated by the intraperitoneal administration of WR-2721 15 min prior to the HN2. This potentiating effect

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was studied by examining a variety of thiols for both potentiating effects against the AKR leukemia and protective effects against normal hematopoietic stem cells (NCFU) for HN2. Twelve different agents were studied which were mainly analogs of cysteamine. The max tolerated dose of each agent was first determined and this dose was administered 15 min before the HN2. All except one of the agents studied demonstrated some protection of NCFU, with the extent of the protection varying from 1.1 for 2-mercaptoethanol to 44 for WR-2721. These indices represent the ratio of the survival of the NCFU with or without thiol pretreatment. When a similar study was done f or the AKR leukemia, both protection from HN2 cytotoxicity as well as potentiation of this cytotoxicity was observed. Initial studies have been done to examine whether a tumor other than the ARK leukemia would demonstrate similar potentiation. L1210 was used. Little potentiation (about 2-fold) was noted when WR-2721 preceded HN2 by 15 min in this tumor model. A variety of thiols have been found to potentiate the cytotoxicity of HN2 in both the AKR and L1210 leukemia models. Potentiation is noted both a for a 15 min and a 6 hr interval although differences were found between the 2 tumors. There was no correlation noted between the ability of the thiols to protect HN2 cytotoxicity against NCFU and their ability to potentiate cytotoxicity in the leukemia models.

298. CHEMICAL MODIFICATION OF CELLULAR RESPONSE TO CALIFORNIUM-252 (MEETING ABSTRACT)

Goud SN, Schroy CB, Magura C, Feola JM, Maruyama Y
Dept. of Radiation Medicine, Univ. of Kentucky Medical Center, Lexington, KY 40536
Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 101, 1985.

The effects of caffeine and dimethyl-sulfoxide (DMSO) on the cytotoxic effects of Cf-252 were studied using human T-1E cells. Cf-252 emits neutrons with a mean energy of 2.3 MeV. Two thirds of the absorbed dose is from neutrons, the remainder from gamma rays. The neutrons have a RBE value of 2 to 10. Exponentially growing cells were exposed for up to 2 hr in suspension to radiation emitted by encapsulated Cf-252 sources. Total Cf-252 was 350 mcg. At the end of each exposure, appropriate aliquots of cell suspension were removed, counted, and plated. DMSO (2M) were present during irradiation and caffeine (2mM) was added immediately after irradiation and was present for 48 hr. Cell survival curves show potentiation of cell killing by caffeine and radioprotection by DMSO. The DMSO results indicate the probability of scavengable free radical killing by Cf-252. The caffeine data indicate that potentially lethal damage exists in the cells after exposure to this high LET radiation source.

299. EFFECT OF VARIOUS PHARMACOLOGICALLY ACTIVE SUBSTANCES ON CYSTAMINE METABOLISM IN TISSUES OF MICE

Tarnopol'skaia LG
No affiliation given
Radiobiologiia; 22(2):246-250 1982

The effects of vasoconstrictor agents (mexamine and ethirone) and an antihypoxic agent (gutimine) on the metabolism of radioprotector cystamine (CA) were studied in male albino mice. Mexamine and gutimine reduced the rate of CA metabolism in the spleen and liver. Ethirone failed to inhibit CA metabolism. These findings indicate that administration of physiologically active substances can enhance the radioprotective effect of CA. (12 Refs)

300. TOXICITY AND RADIOPROTECTIVE EFFECT OF MULTICOMPONENT COMBINATIONS OF SULFUR-CONTAINING SUBSTANCES

Kalistratov GV, Belavina LP, Zherebchenko PG
No affiliation given
Radiobiologiia; 22(5):628-632 1982

Toxicity and radioprotective efficacy of various mixtures of sulfur-containing compounds were studied in random-bred and in (CBA x C57Bl)F1 mice. Multicomponent mixtures provided more effective radiation protection than the individual components alone. The potentiation of the radioprotective effect was not associated with the additive toxicity. (12 Refs)

301. EFFECT OF GLUTAURINE AND ITS DERIVATIVES AND THEIR COMBINATIONS WITH RADIATION PROTECTIVE SUBSTANCES UPON IRRADIATED MICE

Feuer L, Benko G
Chinoin Pharmaceutical and Chemical Works Ltd., H-1325, Budapest, Hungary
Acta Radiol Oncol Radiat Phys Biol; 20(5):319-324 1981

The radiation protective effects of glutaurine (gamma-L-glutamyl-taurine, Litoralon), and of some of its derivatives, as well as of their combinations with substances of the aminoalkyl-thiol group, have been investigated in mice. The results suggest that glutaurine possesses a radiation protective effect in animals irradiated with LD50/30 of roentgen rays and 60Co gamma rays. The compound has a favorable effect also when administered after irradiation. Among the combinations best results were obtained by its simultaneous administration with subminimal doses of S-beta-aminoethyl-isothiuronium (AET) or cystamine. Some of its derivatives also exhibited considerable protection against irradiation with roentgen rays. (Author abstract) (19 Refs)

302. POTENTIATION OF THE PROTECTIVE EFFECT OF SULFUR-CONTAINING RADIOPROTECTORS

Vladimirov VG, Zaitseva TG, Smirnova SM
No affiliation given
Radiobiologiia; 21(6):836-840 1981

Potentiation of the radioprotective effect of cystamine (CA) and aminopropylaminoethylthiophosphoric acid (APAETP) was studied in random-bred albino mice. The animals were subjected to whole-body gamma irradiation (750 rads); 20 min prior to irradiation, the mice were inoculated ip with CA or APAETP alone or in combination with thiourea derivatives (TUD). Analysis of the survival rates, the number of endogenous colony-forming units in the spleen, and the number of nucleated cells in the bone marrow showed that TUD enhanced the radioprotective effect of APAETP and especially of CA. (10 Refs)

303. INEFFECTIVENESS OF 2-MERCAPTOPROPIONYLGLYCINE IN INCREASING SURVIVAL OF MICE AFTER GAMMA IRRADIATION EITHER ALONE OR IN COMBINATION WITH 2-AMIONETHYL ISOTHIURONIUM BROMIDE HYDROBROMIDE

Ghose A, Srinivasan MN
Inst. Nuclear Medicine and Allied Sciences, Probyn Road, Delhi-110007, India
J Radiat Res (Tokyo); 21(3/4):197-203 1980

The radioprotective efficacy of the mixture of the optimum dose of 2-mercaptopropionylglycine (MPG: 20 mg/kg) and suboptimum doses of 2-aminoethyl isothiuronium bromide hydrobromide (AET: 400, 200, or 40 mg/kg) in Swiss A albino mice after 760 R and 1,060 R whole body gamma irradiation was studied. MPG treatment either alone or in com-

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bination with AET did not increase the survival of the mice, compared with control animals. AET at 200 mg/kg rendered excellent protection of the mice after the otherwise lethal dose of 1,060 R radiation. (13 Refs)

304. TOXICITY AND RADIOPROTECTIVE EFFECT OF SOME SULFUR-CONTAINING PROTECTIVE AGENTS DURING THEIR COMBINED PERORAL ADMINISTRATION

Suvorin EV
No affiliation given
Radiobiologiia; 20(5):746-749 1980

Toxicity of amino propyl amino ethylthiophosphate (APAETP), cystaphos, 2-aminoethylisothiouronium bromide hydrobromide (AET), and their various combinations was studied in 425 mongrel mice, whereas radioprotective effects of these agents were studied in 500 hybrid mice. All mice were irradiated in the doses, ranging from 700 to 1,650 rads. The additivity of toxicity was observed when AET was used in combination with either cystaphos or APAETP; this was not observed during the combined use of APAETP and cystaphos. The combined use of APAETP, cystaphos and AET was found to increase the radioresistance of mice irradiated at superlethal doses more than the individual use of these agents did. When this combination was used in mice irradiated at the doses that cause the bone marrow syndrome, their radioprotective effect was not superior to the effect produced by these agents when used alone; however, it was safer than their separate use. (23 Refs)

305. COMBINED TREATMENT WITH APAETP AND OTHER RADIOPROTECTIVE AGENTS

Suvorin EV
No affiliation given
Radiobiologiia; 20(4):595-598 1980

The possibility of enhancing the radioprotective effect of aminopropyl aminoethylthiophosphate (APAETP), using ip administrations of other radioprotectors (S-ethyl isothiuronium, euspiran, and mexamine) was studied in 680 hybrid mice. It was concluded that APAETP efficacy can be increased with the help of other radioprotectors when the former is administered po, and the latter are given ip. (12 Refs)

306. RADIOPROTECTIVE EFFECTIVENESS AND TOXICITY OF ATP, AET AND SEROTONIN APPLIED INDIVIDUALLY OR SIMULTANEOUSLY TO MICE. IV. IDENTIFICATION OF MAXIMUM EFFECTIVE DRUG PROPORTIONS

Benova DK, Putev IKh
Inst. Roentgenology and Radiobiology, Sofia 1156, Bulgaria
Strahlentherapie; 155(6):419-424 1979

Adult male C57BL mice were exposed to total-body radiation (TBR: 850 R) after ip injection of 2-(2-aminoethyl)-2-thiopseudourea 2HBr (AET), ATP, or serotonin (5-HT), singly or in combination. The dose protecting 50% of the mice from death within 30 days (PD(50)) was 166 mg/kg for AET alone, 37 mg/kg for 5-HT alone, and about 1,200 mg/kg for ATP alone. All drug pairs had synergistic radioprotective activity. In mice given ATP-AET, the greatest protection was with 60-70% of the PD50 of ATP and a declining dose (from 22% to 12% of the PD(50)) of AET. ATP plus 5-HT was more effective than ATP-AET. The greatest protection was with 30% of the PD50 of ATP (360 mg/kg) plus 33% of the PD50 of 5-HT (12 mg/kg). Protective activity declined with higher doses of ATP. AET plus 5-HT was the most effective pair. The greatest protection was with 10-20% of the PD50 of AET (17-33 mg/kg) plus declining doses of 5-HT (29% to 19% of the PD50; 11 to 7 mg/kg); the most effective ratios were 1.3-4.0:1. Three-dimensional diagrams of the dose-effect curves were used to predict interactions between the agents for simultaneous triple-agent therapy. The most effective triple combination was 5-6% of the PD50 of ATP (60-72 mg/kg), 9% of the PD50 of AET (15 mg/kg), and 23-24% of the PD50 of 5-HT (8.5-9 mg/kg), with a dose ratio of 7.5-9 (ATP):2 (AET):1 (5-HT). In mice exposed to TBR (850 R) after treatment with the triple combination of ATP (60 mg/kg), AET (15 mg/kg), and 5-HT (9 mg/kg), the 30-day survival rate was 75%, compared to the expected 50%. Doubling of these doses, maintaining the dosage ratio, increased the survival rate to 88%. The most important component of this combination was 5-HT, followed by AET. ATP played a minor role in the triple combination. Enhancement was observed only at ATP doses of less than or equal to 156 mg/kg. (18 Refs)

307. RADIOPROTECTIVE EFFECT OF INHALED EUSPIRAN AND ITS COMBINATION WITH OTHER RADIOPROTECTORS

Solovyov YuA, Zherebchenko PG
No affiliation given
Radiobiologiia; 19(4):623-626 1979

Inhalation of Euspiran (ES) 5-60 min prior to irradiation with Co60 gamma rays (950 R) led to a 45% survival in a test system using CBA x C57BL mice, while inhalation of S-ethyltheironium (S-EIT) prior to irradiation led to a 20% survival. With inhalation of both ES and S-EIT before irradiation the survival was 35%. When the mice were administered aminopropylaminoethylthiophosphate (APAETP: 137 mg/kg, po) 30 min prior to the irradiation, the survival was only 12%, but when this dose of APAETP was used in combination with ES, the survival was 68%. At a higher dose (275 mg/kg), APAETP alone and in combination with ES provided survivals of the irradiated mice of 70% and 90%, respectively. (8 Refs)

308. REPAIR AND BIOCHEMICAL PROTECTION IN LIFE SHORTENING OF MICE EXPOSED TO FRACTIONATED X-IRRADIATION

Maisin JR, Gerber GB, Lambiet-Collier M, Mattelin G
Dept. Radiobiology, C.E.N./S.C.K., B-2400 Mol, Belgium
Radiat Environ Biophys; 15(1):35-45 1978

The radioprotective effect of a mixture of 2-beta-aminoethylisothiouronium-Br-HBr (AET), glutathione, cysteine, mercaptoethylamine, and 5-hydroxytryptamine was determined using BALB/C+ mice which were x-irradiated at regular intervals (7, 15, 30, 60 days) until death with single doses ranged from 300-1,500 R. AET alone was given to a series of mice irradiated on days 30 and 60 only. Control mice and those given AET alone died after a total dose of about 2,000 R. Mice given the mixture of radioprotectors died after a total dose of about 4,000 R. Bone marrow failure and radiopneumonitis were the most frequent causes of death during the first 200 days after the start of irradiation, and glomerulosclerosis and fibrotic conditions the most frequent causes at later times. Using H3-thymidine uptake as a measure of cell proliferation, the av number of nucleated bone marrow cells did not change markedly during early periods after the start of irradiation, but did increase significantly at the time when most animals died. Until a dose of nearly 2,000 R was obtained, the percentage of mice given the mixture of radioprotectors dying from acute bone marrow effects was nearly independent of the previous exposures for the 15, 30, and 60 day intervals, indicating that acute radiation damage in bone marrow is efficiently repaired. The mixture of radioprotectors used is effective against early as well as late radiation damage from fractionated exposure, though the protective

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effects against late damage may be somewhat smaller than against acute damage. (27 Refs)

309. POTENTIATION OF THE RADIOPROTECTIVE EFFECT OF NOREPINEPHRINE AND OTHER PROTECTORS BY VARIOUS BETA-ADRENOLYTICS
Kulinskii VI, Iashunskii VG
Medical Inst., Krasnoiarsk, USSR
Radiobiologiia; 18(5):667-673 1978

Potentiation of the radioprotective effect (RPE) of a series of radioprotectors by various beta-adrenolytics (b-AL) was investigated in CBA mice. The potentiating b-AL compounds included anapriline, N-isopropyl-p-nitrophenylethanolamine, teranol, alfeprol. Animals were inoculated with b-AL, injected sc or ip 15 min later with radioprotectors (10 ml/kg), and irradiated 15 min later with 800 rads. The b-AL caused a 3.2 x increase in the RPE of norepinephrine. The b-AL potentiated the RPE of both direct and indirect radioprotectors. (16 Refs)

310. RADIOPROTECTIVE EFFECTIVENESS AND TOXICITY OF ATP, AET AND SEROTONIN APPLIED INDIVIDUALLY OR SIMULTANEOUSLY TO MICE. III. RADIOPROTECTIVE EFFECTS OF PAIR COMBINATIONS
Benova D
Inst. Roentgenology and Radiobiology, Sofia 1156, Bulgaria
Strahlentherapie; 153(8):566-569 1977

The radioprotective effects of paired combinations of ATP, serotonin, and 2-(2-aminoethyl)-2-thiopseudoharnstoff dihydrobromid (AET) were investigated in male C57BL mice. Paired combinations of the drugs were administered ip 8 min prior to irradiation with 850 R, and 30-day survivals were scored for various drug dose ratios. For ATP-AEP, protection increased with the amount of ATP in the combination and the max protective effect was obtained with an ATP:AET ratio of 11:1 (720 mg/kg ATP and 66 mg/kg AET), which resulted in an 80% survival. The above ATP and AET doses corresponded to 60% and 40%, respectively, of the protectant dose affording 50% survival (PD50). The most protective ATP-serotonin combination consisted of 480 mg/kg ATP (40% PD50) and 19 mg/kg serotonin (50% PD50) and resulted in an 85% survival. The protective effect of this combination again increased with increasing ATP concentration, although only up to a certain ATP level (480 mg/kg), beyond which no increase in protection was observed. Max synergism was displayed by AET-serotonin combinations, with the most effective combination being 33 mg/kg AET (20% PD50) and 7 mg/kg serotonin (20% PD50), which resulted in a 95% 30-day survival. Synergistic action between components of the above combinations was evidenced by the fact that a 50% radioprotective effect was ensured at sums of individual protectant PD50 percentages of less than 100. The above data also indicate that ATP is a promising component for such radioprotective combinations. (13 Refs)

311. TUMOR REJECTION IN EXPERIMENTAL ANIMALS TREATED WITH RADIOPPROTECTIVE THIOLS
Apffel CA, Walker JE, Issarescu S
Ira T. Nathanson Res. Lab., Mass. Dept. Public Health, Pondville Hosp., Walpole, Mass.
Cancer Res; 35(2):429-437 1975

The effect of 12 daily i.p inj of 1 of 5 different radioprotective thiols (1 mg/day) on tumor cell rejection or inhibition of tumor cell growth was studied in several strains of inbred mice bearing 5 different types of solid tumors. All 5 thiols, which are of the mercaptoalkylamine type, produced either inhibition of tumor cell growth or tumor necrosis with sloughing (oncodieresis) resulting in full recovery of the animals. One of the thiols, cysteamine, was active in its native, unsubstituted form, but showed no ability to affect oncodieresis when either the amino or alkyl group, or both, were alkylated. Mercaptopropylamine, the 3-carbon homologue of cysteamine, was less active, while cystamine, a disulfide dimer of cysteamine that contains no free reactive sulfhydryl group, showed no antitumor effect. Thioglycerol, which lacks a terminal amino group, had only negligible oncodieretic activity. Tumor rejection occurred much less frequently if thiol treatment was started 7 d after tumor cell inocn rather than 1 d after. Tumor rejection occurred more effectively in males than in females. Combined thiol treatment or simultaneous inj of any 1 with other radioprotectants (L-cysteine, glutathione, dimethyl sulfoxide or reserpine) resulted in decreased ability to reject tumors. Tumor rejection was enhanced when the phosphorylated thiols, S-2-(3-aminopropylamino) ethylphosphorothioic acid or S-(2-ethylguanidine) phosphorothioic acid, were given simultaneously with serotonin. However, serotonin and the nonphosphorylated compounds, S-2-aminoethylisothioronium bromide or cysteamine, were not synergistic. These results suggest that binding of both free thiol and amino groups to intra-and/or extracellular membranes is necessary for oncodieretic activity of the substances studied. (24 refs)

VI.

FOOD ADDITIVES AND DIETARY FACTORS

312. PROTECTIVE EFFECT OF VITAMIN A AGAINST LEWIS LUNG CARCINOMA TRANSPLANTED INTO MICE AFTER WHOLE BODY IRRADIATION (MEETING ABSTRACT)
Mendecki J, Friedenthal E, Seifter E, Davis L
Radiation Therapy Dept., Montefiore Medical Center/Albert Einstein Coll. of Medicine, Bronx, NY
Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 113, 1985.

Survival after Whole Body Irradiation (WBI) and percentage of 'takes' of Lewis Lung carcinoma transplanted subcutaneously were followed in two groups of mice: one maintained on supplemental Vit A diet and the other on normal laboratory chow. In each group, one of four subgroups received WBI in doses of 450, 550, 650 and 800 cGy respectively. Vit A was started 3 days before WBI. Survival time was found to be inversely proportional to the dose of WBI in each subgroup but was prolonged in the Vit A group. The percentage of tumor 'takes' correlated directly with the dose of radiation, but was markedly decreased in the Vit A group. The drop in white blood cell and platelet counts seen after WBI was also found to be of lesser magnitude in the Vit A group. It is suggested that supplemental Vit A exerts a protective effect against some of the toxic aspects of WBI in mice.

313. RADIOPROTECTION: EFFECTS OF NUTRITIONAL FACTORS ON ENDOGENOUS PROTECTIVE ENZYMES AND SURVIVAL OF IRRADIATED MICE (MEETING ABSTRACT)
Jacobs AJ, Weiss JF
Biochemistry Dept., Armed Forces Radiobiology Res. Inst., Bethesda, MD 20814
Thirty-Second Annual Meeting of the Radiation Research Society, March 25-29, 1984, Orlando, Florida, p. 106, 1984.

The nutritional relationship of vitamin E and selenium, with respect to their antioxidant activities, may be related in part

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to glutathione peroxidase activity and related enzymatic pathways. Previous studies in our laboratory have indicated that protection or induction of glutathione peroxidase activity may have a role in radioprotection. In the present studies, CD2F1 male mice were given increased amounts of Fe and/or Zn in their drinking water (50% or 100% above normal dietary levels). In general, increased intake of these minerals resulted in protection against weight loss and increased survival, including improved Kaluszyner survival coefficients calculated 30 days after 800 or 850 rad exposures. There is little difference in the results between the treated groups. No changes in the glutathione peroxidase or catalase activities in tissues were observed when either Zn or Fe were added to the diet. The addition of three times the normal level of vitamin E to the diet did not improve the results of the treatments where increases in Zn, Fe, or both were given. Additional studies are in progress to determine the combination of vitamins and minerals that will provide the best radioprotection and to determine the biochemical basis for increased protection.

314. VITAMIN A AND RADIOPROTECTION (MEETING ABSTRACT)

Mendecki J, Shen RN, Friedenthal E, Rettura G, Levenson SM, Seifter E

Montefiore Medical Center, Albert Einstein Coll. of Medicine, Bronx, NY

Thirty-Second Annual Meeting of the Radiation Research Society, March 25-29, 1984, Orlando, Florida, p. 113, 1984.

Vitamin A was shown to reduce the toxicity of whole body x-irradiation in C3H and Swiss mice. Vitamin A mixed with Purina Laboratory Chow (150000 IU/kg) was administered to the experimental groups for 3 days prior to exposure to 550 cGy of whole body radiation from a 60 Cobalt source. Control groups submitted to the same radiation had no supplementary Vitamin A in the chow. Survival time of the animals fed Vitamin A was significantly longer and the post-radiation depletion of platelets and white blood cells was much less marked than in the controls. It is suggested that Vitamin A exerts a protective effect against certain manifestations of radiation toxicity.

315. RADIATION RESISTANCE IN MICE INCREASED FOLLOWING CHRONIC APPLICATION OF LI2CO3

Vacek A, Sikulova J, Bartonickova A

Institute of Biophysics, Czechoslovak Academy of Sciences, Brno.

Acta Radiol kOncol; 21(5):325-30 1982

In experiments on strain H mice the increased radiation resistance of mice was analysed after three weeks' feeding with a diet including Li given as lithium carbonicum. The concentration of Li in the serum during the first three days of feeding was increased to 0.5 mmol/l and remained at that level to the end of feeding. The application of Li increased the overall number of stem cells in the spleen by 80 per cent compared with the control group. D0 of the line of dependence of the number of endogenous colonies on radiation dose increased following Li application by 1.2 Gy compared with controls. The proliferation activity of haemopoietic stem cells observed 90 min after injection of hydroxyurea was, after 21 days feeding with a mixture containing Li, increased by 200 per cent. The results support the idea that the increased radiation resistance of mice following feeding with Li salts before irradiation may be due to the increased content and resistance of the haemopoietic stem cells, as well as activation of granulopoiesis.

316. [ANTIRADIATION AND LEUKOPOIETIC ACTIVITIES OF TEA PREPARATIONS]

Chen H

Naval Medical Coll, People's Republic of China

Zhonghua Fangsheyixue Yu Fanghu Zazhi; 2(3):61-63 1982

Radiation protective effects are described for several tea preparations in both animals and humans. The most active preparation (extract 7369) was a freeze-dried total extract of tea prepared with boiling water. Extract 7369 markedly prolonged the survival of animals that received lethal doses of radiation. It reduced radiation injuries in cancer patients receiving radiotherapy, especially in the prevention of radiation-induced leukopenia. (9 Refs)

317. RESTORATION OF RADIATION INJURY BY GINSENG. I. RESPONSES OF X-IRRADIATED MICE TO GINSENG EXTRACT

Takeda A, Yonezawa M, Katoh N

Dept. Medicine and Hygiene, Radiation Center Osaka Prefecture, Shinke-cho, Sakai, Osaka 593, Japan

J Radiat Res (Tokyo); 22(3):323-335 1981

The radioprotective effect of ginseng extract (GE) in JCL-ICR mice and hematological recovery of irradiated native and splenectomized mice were studied. Six-wk-old male mice were irradiated with 720 or 550 R. Within 3 min after irradiation, mice were injected ip with GE dissolved in 0.2 ml physiological saline. Control mice were injected only with saline after irradiation. Injection of 5.0 mg GE 2.5 hr before or after exposure to 720 R was significantly efficacious, but injection 1 day after treatment was not. Administration of 5.5 mg GE 2 or 1 day prior to irradiation was more efficacious than administration immediately after irradiation. The 30-day survival ratio of mice irradiated with 720 R was 5, 45, 75 and 82.5% for mice injected with 0, 1.8, 3.4, and 6.8 mg GE, respectively. The difference between control and GE groups was significant. Splenic wt of irradiated mice decreased to approx 1/3 normal on days 2-10 in the control group. The decrease was less in the GE group. Thymic wt decreased after irradiation by approx 30% from day 0 to day 30. Recovery of thymic wt was not stimulated by GE extract. GE-stimulated recovery of splenic DNA, and of thrombocyte and erythrocyte counts was observed; GE did not markedly affect leukocyte counts. GE increased the 30-day survival ratio of splenectomized mice. Only thrombocyte counts after exposure were stimulated by GE in splenectomized mice. Recovery of thrombocyte counts after exposure is assumed to be one of the most important factors in restoration after bone marrow death. (10 Refs)

318. RESTORATION OF RADIATION INJURY BY GINSENG. II. SOME PROPERTIES OF THE RADIOPROTECTIVE SUBSTANCES

Yonezawa M, Katoh N, Takeda A

Dept. Medicine and Hygiene, Radiation Center Osaka, Shinke-cho, Sakai, Osaka 593, Japan

J Radiat Res (Tokyo); 22(3):336-343 1981

Some properties of the radioprotective substance ginseng extract (GE) were studied in male 4-wk-old JCL-ICR mice. Prior to injection GE was dissolved in physiological saline and insolubles discarded after centrifugation. Mice injected with only physiological saline served as controls. The 30-day survival ratio was measured in both groups. Methanol-soluble GE did not protect the irradiated animals. Acid or alkali (0.12 N) inactivated GE at 60 C. GE radioprotective activity was stable after heating in physiological saline at pH 7 in a boiling-water bath for 15 min. GE was separated into two fractions by CM-cellulose column chromatography. Fraction CM-A was significantly efficacious at p less than 0.05, and

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CM-B was effective at p less than 0.001; doses were proportional to yield. UV spectrum and biuret tests suggested the presence of protein in the CM-B fraction. Supernatant obtained after heating the CM-B solution at pH 7 was separated into fractions G-I, G-II, and G-III by gel chromatography with a Sephadex G-75 column. G-I (0.44 mg/animal) and G-III (0.84 mg/animal) were significantly efficacious, but G-II (0.47 mg/animal) was not. The active component in ginseng had been thought to be ginseng saponin. Examination of the methanol-soluble fraction showed that the radioprotective component of GE is not saponin. Purification of the radioprotective substance is needed to clarify the chemical structure. (9 Refs)

319. RADIOPROTECTIVE EFFECT OF PROPYL GALLATE AND BUTYLATED HYROXYANISOL

Ramos-Damian M, Acosta-Ruiz R, Hernandez-Delgado J, Vazquez-Valls E, Gomez-Estrada H
(c/o Gomez-Estrada) Apartado Postal 1-3838, Guadalajara, Jalizco, Mexico
Arch Invest Med (Mex); 12(3):421-430 1981

The radioprotective effects of some commonly used food antioxidants were investigated. The 40 BALB/C mice, that received 600 rads gamma irradiation, died 17.12 +-7.82 days later. The 13 mice injected with 5 mg n-propyl gallate (NPG) 24.5 hr before irradiation survived more than 90 days. The same effect was observed in groups of 13 rats after injecting 10 mg butylated hydroxytoluene (BHT). Increasing the irradiation dose to 800 rads NPG, BHA or BHT did not have radioprotective effect in the doses used. The protected animals were preserving more hematopoietic cells in the bone marrow and had less chromosome fractures. Some food antioxidants exhibit radioprotective effect that was not investigated before. (12 Refs)

320. EVALUATION OF HIGH-DOSE VITAMIN E AS A RADIOPROTECTIVE AGENT

Rostock RA, Stryker JA, Abt AB
Div. Radiation Oncology, M. S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033
Radiology; 136(3):763-766 1980

Sixty male Sprague Dawley rats were randomly divided into six equal groups and given 0, 1,500 rads (15 Gy), and 2,000 rads (20 Gy) whole thoracic irradiation from a cobalt-60 source via an anterior portal. Thirty animals received a 2.5% vitamin E diet for 2 wk prior to irradiation and, in addition, each was given a single ip injection of water-soluble alphaT (150 mg) 4 hr prior to irradiation. Serum vitamin E levels were 646 +-76 ug/ml for vitamin E groups and 6.0 +-2.4 ug/ml for controls. Comparison of the 180-day survival curves and histologic studies performed on the lungs and hearts of the surviving animals showed no statistically significant difference between the vitamin E and control group. (Author abstract) (19 Refs)

321. PREVENTIVE-THERAPEUTIC ROLE OF VITAMIN FROM A B-MESOINOSITOL GROUP DURING RADIATION SICKNESS AGAINST A BACKGROUND OF DAIRY-EGG DIET

Perepelkin SR, Egorova ND
I. M. Sechenov First Medical Inst., Moscow, USSR
Radiobiologiia; 20(1):137-139 1980

The efficacy of a dairy-egg diet supplemented by vitamins of the mesoinositol group (1, 2.5 and 5 mg/rat, po, daily, for 25 days before and 30 days after irradiation) was studied in random-bred albino rats subjected to a whole body irradiation with x-rays (600 R). Mesoinositol administration at 1, 2.5 and 5 mg/rat increased the survival rate of rats with radiation sickness to 84.5%, 83.3%, and 70.0%, respectively, compared with 75.7% in rats who received the dairy-egg diet alone, and 30.3% in rats who received standard physiological diet. (10 Refs)

322. SYSTEMIC PROTECTION AGAINST RADIATION. III. INCREASED INTESTINAL RADIORESISTANCE IN RATS FED A FORMULA-DEFINED DIET

Pageau R, Bounous G
Dept. Nuclear Medicine and Radiobiology, Centre Hospitalier Universitaire, Universite de Sherbrooke, Sherbrooke, Quebec, Canada
Radiat Res; 71(3):622-627 1977

The effect of diet on intestinal radioresistance was studied. Male Sprague-Dawley rats fed either laboratory chow or elemental diet 3 received single dose abdominal irradiation of 850 to 1300 rad. Animals fed diet 3 were able to withstand higher doses of radiation than those given laboratory chow. With the latter group, 40% mortality was observed following a dose of 1000 rad, while 0% mortality was recorded in the diet 3-fed group. Computation, using probit regression lines, of the doses giving 10, 50, and 90% mortality/8 days indicated that the radioprotective action of the diet was greatest at lower mortality levels. Dietary protection ratio (DPR) values of 1.12, 1.06, and 1.00 were obtained at the 10, 50, and 90% mortality levels, respectively. The lower DPR values obtained with higher radiation doses were associated with a steeper slope of the regression line obtained with the group fed diet 3. In animals fed diet 3 rather than laboratory chow, H3-thymidine incorporation and mitotic activity were both enhanced especially in the duodenum, jejunum, and ileum. Increased intestinal radioresistance may be of practical significance in the radiotherapeutic management of tumors. (21 Refs)

323. SYSTEMIC PROTECTION AGAINST RADIATION. I. EFFECT OF AN ELEMENTAL DIET ON HEMATOPOIETIC AND IMMUNOLOGIC SYSTEMS IN THE RAT

Pageau R, Lallier R, Bounous G
Department of Nuclear Medicine, Centre Hospitalier Universitaire, Universite de Sherbrooke, Sherbrooke, Quebec, Canada
Radiat Res; 62(2):357-363 1975

The effects of normal laboratory pellet food and the Mead-Johnson elemental diet 3200-BD on the survival of Sprague-Dawley rats given a total body dose of 700 rads of 60 Co gamma-radiation were determined. The diets were also compared with respect to their effects on [3-H]-thymidine incorporation by hematopoietic tissues, on activation of the immune system by SRBC (108 cells, ip), and on serum proteins. Only 6% of the 16 rats fed the food pellets survived whole-body exposure to 700 rads and the mean survival time was nine days. In contrast, 73% of the 15 rats fed the elemental diet for a week before irradiation survived and the mean survival time was 59 days. However, none of 15 animals given the elemental diet after radiation survived, and the mean survival time of 6.1 days was significantly shorter than that obtained with the normal diet. In animals fed the normal diet, [3H]-thymidine incorporation was highest in the mesenteric lymph nodes followed by the spleen, thymus, and bone marrow. This same sequence was significantly higher in spleen (162%), thymus (181%), and bone marrow (164%) of these rats compared with the pellet-fed controls. Antibody titers seven days after activation of the immunologic system by SRBC were 179 in animals given the elemental diet and 89 in those given the pellets. The elemental diet also produced a significant increase in the serum alpha2 fraction. These results confirm the reported radioprotective action of the Mead-Johnson diet and demonstrate that feeding of the

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diet is associated with enhanced cellular proliferation in hematopoietic tissues and better response to antigen stimulation.

VII.

SYNTHESIS, CHEMICAL AND PHYSICAL ANALYSES

324. RADIOPROTECTION OF EMT6 TUMOR BY A NEW CLASS OF RADIOPROTECTORS BASED ON A PSEUDO-PEPTIDE CYSTEAMINE COMBINATION

Lespinasse F, Oiry J, Fatome M, Ardouin P, Imbach J, Malaise EP, Guichard M
Laboratoire de Radiobiologie Cellulaire, Unite Inserm 247, Institut Gustave-Roussy, Villejuif, France.
Int J Radiat Oncol Biol Phys; 11(5):1035-8 1985

Although WR-2721 preferentially protects normal tissues against irradiation, it seemed desirable to find other drugs presenting a lower toxicity and the same radioprotective properties. A new compound, I 102, was selected; it was characterized on one hand by a coupling between cysteamine and an amino-acid, and on the other hand by an acetyl-group, which protects the thiol function. The effects of WR-2721 and of I 102 were studied on EMT6 tumors grafted on BALB/c mice. Whatever the size of the tumor, the cell survival increased as a function of the time elapsed between the injection of I 102 and the end of the irradiation (TI). In contrast, the radioprotection afforded by WR-2721 was found to be independent of TI. The survival curves suggest that, like WR-2721, I 102 protects essentially oxygenated cells.

325. MEASUREMENT OF WR-2721, WR-1065, AND WR-33278 IN PLASMA

Fahey RC, Newton GL
Department of Chemistry, University of California, San Diego, La Jolla 92093.
Int J Radiat Oncol Biol Phys; 11(6):1193-7 1985

Alkaline phosphatase was used in developing two new assays for WR-2721; one involved simple spectrophotometric titration with Ellman's reagent and the other was based upon HPLC analysis of a monobromobimane derivative. Both methods gave acceptable results when applied to whole plasma. Assays for WR- 1065 and disulfide forms of the drug were also developed but were found to give unreliable results with whole plasma owing to apparent rapid reaction of these drug forms with plasma constituents. The methods were applied to the analysis of blood samples in rat 0-70 min after i.v. injection of WR-2721.

326. IN VIVO NMR SPECTROSCOPY OF [C-13]-WR3689: A NEW APPROACH FOR NON-INVASIVELY STUDYING THE MECHANISM OF RADIOPROTECTION BY PHOSPHOROTHIOATES (MEETING ABSTRACT)

Golden RN, Grunbaum Z, Wade RA, Haynor DR, Drobny G, Krohn KA
Dept. of Radiology, Univ. of Washington, Seattle, WA 98195
Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-17, 1985.

NMR spectroscopic imaging may be the only accurate technique for following the biochemical reactions of phosphorothioates in vivo and therefore an NMR probe that fit into an 89 mm bore, 4.7 tesla magnet has been built. The probe holds an alive and awake mouse in a velcro pouch next to a surface coil that is sensitive to a sample vol of about 0.5 g and is triple-tuned to H-1, P-31 and C-13 frequencies. The position of the surface coil next to the animal is fully adjustable. [C-13]-WR3689 was synthesized as a phosphorothioate tracer in which the enriched stable C-13 is located next to the sulfur atom. The chemical shift of this C-13 resonance is sensitive to the oxidation state of the neighboring S atom and can be used to identify the chemical group on the opposite side of the sulfur. The shift is only very slightly affected by pH. This probe has been used for quantitating chemical changes in phosphorothioates and their derived thiols and disulfides in the presence of endogenous thiols. The NMR probe positioned over the liver was used to follow chemical changes in [C-13]- WR3689 following ip injection at 450 mg/kg. The surface coil is sufficiently sensitive to give accurately integratable NMR peaks with 15 min of data collection. Spectra have been collected serially from 15 min to an hr. Initial results show that phosphorothioates are dephosphorylated and undergo subsequent reactions to a much lesser extent than has been measured with invasive chromatographic assays of the chemical form of extracted radioactive [S-35]-WR3689.

327. FEASIBILITY OF USING 31P NMR SPECTROSCOPY TO STUDY PHARMACOKINETICS OF THE RADIOPROTECTOR, WR-2721 (MEETING ABSTRACT)

Sridhar R, Crossley C, Robinson RD, Schmidt PG
Oklahoma Medical Res. Foundation, 825 Northeast 13th St., Oklahoma City, OK 73104
Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-20, 1985.

We have used 31P nuclear magnetic resonance spectroscopy (31P NMR) for in vitro and in vivo detection of WR-2721 (S-2-(3-aminopropylamino)ethylphosphorothioic acid), and for studying the dephosphorylation of this phosphorothioate. The NMR signal due to the phosphorus nucleus of the phosphorothioate group in WR-2721 occurs in a region of the spectrum where there is no interference from the phosphorus compounds usually found in tissues and tumor. In vitro 31P NMR was used to monitor dephosphorylation of WR-2721 by dilute HCl and by Balb/c mouse liver homogenates. WR-2721 was given at a dose of 400 mg/kg to a Balb/c mouse by intramuscular injection into the thigh and the muscle was monitored at the point of injection using a surface coil to obtain 31P NMR spectra before and at 20, 40 and 80 min after drug injection. Similarly, the same dose of WR-2721 was injected directly into an EMT6 tumor growing in the hind leg of a Balb/c mouse and the NMR spectra of the tumor was recorded before and at 20, 40 and 80 min post injection. The phosphorothioate signal was clearly seen in every spectrum recorded after administration of WR-2721. This signal which was most intense in the spectra acquired at 20 min after drug injection, decreased progressively in the spectra acquired at later times. The rate of loss of the phosphorothioate signal of WR-2721 was significantly faster from the well vascularized muscle compared to that from the poorly vascularized tumor. In the case of tumor, the loss of the phosphorothioate signal of WR-2721 was accompanied by simultaneous increase in inorganic phosphate signal. Such an increase in inorganic phosphate signal was not seen in the spectra from muscle. These results suggest that dephosphorylation of WR-2721 can occur in the EMT6 tumor. In vivo 31P NMR spectroscopy provides a noninvasive technique for studying pharmacokinetics of WR-2721. 31P NMR complements the other techniques that are currently available for studying pharmacokinetics of WR-2721.

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328. A PROCEDURE FOR THE COMBINED MEASUREMENT OF ETHIOFOS, WR 1065 AND DISULFIDES OF WR 1065 (MEETING ABSTRACT)

Huelle BK, Swynnerton NF, Mangold DJ
Southwest Res. Inst., 6220 Culebra Rd, PO Drawer 28510 San Antonio, TX 78284
Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-22, 1985.

Bioavailability of the radioprotective drug ethiofos (WR 2721) may best be evaluated by a combined measurement of the drug itself and its various metabolic forms. It has been shown that one of the drug's metabolites, 2-(3-aminopropylamino)ethane thiol (WR 1065), binds to plasma proteins in the form of mixed disulfides and may also be present as its symmetrical disulfide. We have developed an analytical method to quantitatively convert ethiofos, disulfides of WR 1065 and WR 33278 to WR 1065 which is then measured by HPLC separation/electrochemical detection. Plasma samples containing the internal standard (WR 1729) were heated with a 30% tributylphosphine solution in chloroform and HPLC mobile phase (2.0 M monochloroacetic acid, 6% acetonitrile, 0.006 M camphor sulfonic acid, pH 3) to 70 C for 30 min. After cooling and centrifugation, 50 uL of the supernatant (aqueous phase) was injected onto the HPLC system. Analyses of samples spiked with various combinations of ethiofos, WR 1065, and WR 33278 showed an av conversion of 98%. Ethiofos was administered intravenously to Rhesus monkeys in pharmacokinetic studies. These studies indicated that free WR 1065 measured by this method exceeded ethiofos concentrations by greater than 100-fold at later times, suggesting the existence of large concentrations of mixed disulfides.

329. HPLC ASSAY FOR ETHIOFOS IN PLASMA: APPLICATION TO PHARMACOKINETICS IN THE BEAGLE DOG (MEETING ABSTRACT)

Swynnerton NF, Mangold DJ, Ludden TM
Southwest Res. Inst., San Antonio, TX 78285
Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 48, 1985.

An HPLC assay for ethiofos [S-2-(3-amino-propylamino)ethyl phosphorothioate, WR 2721] in plasma is presented. Its application to the development of pharmacokinetic parameters following IV administration of the drug to beagle dogs is demonstrated and preliminary pharmacokinetics of four dosings were presented. Following a dose of 150 mg kg(-1), the plasma concentration versus time profile was best described by a two-compartment pharmacokinetics model. Mean pharmacokinetic parameters were: Terminal elimination half-life = 16.0 min, vol of central compartment = 129 mL kg(-1), and clearance = 11.0 mL min(-1) kg(-1).

330. HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC ANALYSIS AND PRELIMINARY PHARMACOKINETICS OF DI-S-2(3-AMINOPROPYLAMINOETHANE DISULFIDE) (WR 33278) IN THE BEAGLE (MEETING ABSTRACT)

McGovern EP, Steele PD, Mangold DJ, Ludden T
Southwest Res. Inst., San Antonio, TX 78284
Thirty-third Annual Meeting of the Radiation Research Society. May 5-9, 1985, Los Angeles, California, p. 98 1985.

Di-S-2-(3-aminopropylamino)ethane disulfide (WR 33278) is a metabolite of the radioprotective drug ethiofos. The separation of WR 33278 from other endogenous plasma thiols and disulfides and its quantitation in plasma has been achieved using HPLC analyte separation combined with dual series Hg/Au electrode amperometric detection. Sample preparation for analysis involves internal standard addition [di-S-2-(5-aminopentylamino)ethane disulfide (WR 149024)], protein precipitation and direct injection of 50 L of supernatant. The analyte elutes from a C-8 reverse phase column in only 16 min and the method allows for the simultaneous determination of WR 1065 as well. The detector response is linear over the range 0.5 100 g/mL and the estimated limit of sensitivity is approx 0.1 g/mL plasma. Preliminary pharmacokinetics in the beagle dog (16 mg/kg, IV) shows the drug is rapidly eliminated, while detectable levels of WR 1065 appear very quickly and are profiled during the entire experimental period.

331. PULSE RADIOLYSIS STUDIES OF WR-1065

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Department of Radiology, School of Medicine, University of California, San Diego, La Jolla.
Int J Radiat Oncol Biol Phys; 10(9):1533-6 1984

WR-1065, the dephosphorylated sulfhydryl form of WR-2721 has been suggested as the metabolite responsible for the radioprotective abilities of the latter and as being active during the radiation chemical stage of damage production. Hence this study was performed to determine some of the radiation chemical parameters of the compound. Pulse radiolysis techniques, developed for use with SH compounds, were employed in the current work: Three systems were used to attempt to measure the rate constant for reaction of OH. radicals with WR-1065; (a) Competition with phenylalanine, in which the decrease in the amount of RSSR- caused by the addition of phenylalanine is monitored; this failed because of the absence of an absorbance attributable to RSSR-. (b) Competition with 2,2'-Azinobis-(3-ethylbenzthiazoline-6-sulfonate) (ABTS), monitoring the decrease in OH. induced ABTS absorbance caused by WR-1065 addition. This was unsuccessful due to reaction of RS. with ABTS. (c) Competition with CNS-, observing the decrease in (CNS)-2 caused by WR-1065 addition indicates that the second order rate constant for reaction of OH. with WR-1065 is 9.2 +/- 0.3 X 10(9) M-1 s-1. To investigate the ability of WR-1065 to react with DNA radicals the yield of ABTS radicals was monitored in a situation where DNA scavenges 50% of the OH. radicals in the presence of ABTS (20%) and WR-1065 (30%). DNA radicals were shown not to react with ABTS but WR-1065 radicals do, the absence of additional ABTS absorbing species indicates that DNA radicals do not react with WR-1065 under the experimental conditions used. An attempt was made to investigate the possibility that WR-1065 is concentrated close to DNA macromolecules in solution: The rate constant for reaction Br2- with WR-1065 was measured in the presence and in the absence of excess DNA (with which Br2- was not observed to react). The observed rates of reaction were independent of the presence of DNA indicating that the latter does not affect the availability of WR-1065 for reaction with Br2- radical. Reaction of WR-1065 with Br2- was used as a probe for determining the pK of the SH group. The rate of reaction increases from 1.8 X 10(8) M-1 s-1 at pH 6.3 to 1.6 X 10(9) M-1 s-1 at pH 8.4, the mid-point of the increase indicates a pK of 7.3.

332. ANALYSIS OF S-35 LABELED WR-2721 AND ITS METABOLITES IN BIOLOGICAL FLUIDS

Anderson KW, Krohn KA, Grunbaum Z, Phillips RB, Mahler PA, Menard TW, Spence AM, Rasey JS
Dept. of Radiology, School of Medicine, University of Washington, Seattle.
Int J Radiat Oncol Biol Phys; 10(9):1511-5 1984

Studies with WR-2721 and related compounds have been hindered by the lack of a suitable assay for the drug and its major metabolites. We have developed a chromatographic method which requires no derivatization for the separation

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and detection of WR-2721, the free thiol, its symmetrical disulfide and other mixed disulfides. Our procedure involves ion-pairing for separation of ionizable compounds by causing polar molecules to become more lipophilic and hence separable using reverse phase HPLC. Detection is based upon liquid scintillation counting of S-35 incorporated during the synthesis of the parent compound. This method requires no pre-column preparation of samples and, by detecting the S-35 label, eliminates the chance that a coeluting species could interfere with detection, as might occur with post-column derivatization. Chromatography was done using a 10 micron C8RP column and 35% MeOH/65% 0.0113M NaH2PO4, 0.005 M hexanesulfonate, pH 5.9, flowing at 1 ml/min. Half-minute fractions were collected into scintillation vials for counting. Retention volumes for the various compounds were: column breakthrough (3.5 ml), WR-2721 (4.5 ml), WR-1065 (9 ml), and WR-33278 (24 ml). This analytical technique employing radiotracers can be used to study radioprotective mechanisms by time dependent measurements of the tissue distribution and chemical form of labeled drug. Such chemical information can then be correlated with biological measures of radiation protection.

333. HPLC ASSAY FOR 2-(3-AMINOPROPYLAMINO)ETHANETHIOL (WR-1065) IN PLASMA

McGovern EP, Swynnerton NF, Steele PD, Mangold DJ
Southwest Research Institute, Chemistry and Chemical Engineering Division, San Antonio, TX.
Int J Radiat Oncol Biol Phys; 10(9):1517-20 1984

A high pressure liquid chromatography (HPLC) plasma assay for WR-1065 is described which is both precise (coefficient of variation less than 5%) and accurate (% average deviation less than or equal to 6.1) throughout the concentration range from 1 to 500 micrograms/mL of plasma. The analyte is separated by HPLC and detected with a thiol specific electrochemical transducer cell. The detector response is linear over the ranges 1 to 10 micrograms/mL (R2 = 0.995), 10 to 100 micrograms/mL (R2 = 0.995), and 100 to 500 micrograms/mL (R2 = 0.974). The absolute retention times for WR-1065 and WR-1729 are 9 and 12 minutes, respectively. The assay uses 100 microL of plasma and requires a total chromatography cycle time of 40 minutes. The method has been found suitable for the determination of WR-1065 in plasma from a beagle dog after i.v. administration of S-2-(3-aminopropylamino)ethyl phosphorothioate (WR-2721).

334. AN IMPROVED HPLC ASSAY FOR S-2-(3-AMINOPROPYLAMINO)ETHYL PHOSPHOROTHIOATE (WR-2721) IN PLASMA

Swynnerton NF, McGovern EP, Nino JA, Mangold DJ
Southwest Research Institute, Chemistry and Chemical Engineering Division, San Antonio, TX.
Int J Radiat Oncol Biol Phys; 10(9):1521-4 1984

An HPLC assay is presented for the detection and quantitation of the radioprotective drug S-2-(3-aminopropylamino)ethyl phosphorothioate (WR-2721, ethiofos) present in plasma. Improved selectivity and a 40-fold increase in sensitivity have been demonstrated over the method previously reported by this laboratory. Using precolumn derivatization with fluorescamine and S-3-(4-aminobutylamino)propyl phosphorothioate (WR-80855, a homolog of WR-2721) as the internal standard, drug levels of 0.05 to 1000 micrograms/mL were determined with excellent precision (CV less than or equal to 5% over the concentration range). An isocratic mobile phase of acetonitrile/ethanol/water (16:7:77) modified with 0.01 M tetrabutylammonium phosphate eluted the drug and the internal standard from the C-18 reverse-phase column in 23 minutes and 26 minutes, respectively. Detector response was linear over the entire range. The assay uses 150 microL of plasma and requires a total chromatography time of about 50 minutes. The method was found suitable for pharmacokinetic studies in a preliminary experiment with a beagle dog in which no interferences due to plasma constituents or drug metabolites were observed.

335. SOME ELECTROSTATIC ASPECTS OF THE INTERACTION BETWEEN DNA OR LIPIDS AND WR 2721 OR HIS METABOLITE WR 1065 (MEETING ABSTRACT)

Vasilescu D, Rix-Montel MA, Kranck H, Broch H, Savant-Ros E
Biophysics Lab., I.P.M., Nice-Univ., Parc Valrose, Nice, France
Molecular Basis of Cancer: An Interdisciplinary Discussion on Basic and Applied Aspects of Cancer, May 30-June 2, 1984, Buffalo, New York, Roswell Park Memorial Institute, p. 13, 1984.

WR 2721 is the phosphorylated aminothiol NH2-(CH2)3-NH-(CH2)2-S-PO3H2. This molecule is known as the most effective radioprotector. On another hand, this drug is a selective protector against ionizing radiation of normal and malignant tissues and it is also able to increase the potentiality of cancer therapy with cis-platin. WR 1065 - the free sulfhydryl part of WR 2721 - [NH2-(CH2)3-NH-(CH2)2-SH] is the metabolic fraction that penetrates the cell membrane and can interact with the nucleus. In this study, we present both experimental and theoretical results concerning the electrostatic properties of these drugs and their interaction with DNA or with synthetic lecithin dipalmitoylphosphatidylcholine (DPPC). When WR 2721 and WR 1065 are dissolved in water or in neutral salt solutions like NaCl, they take a dicationic form for WR 1065 and a dicationic-dianionic form in the case of WR 2721. By spectrophotometry we have demonstrated that when DNA interacts with WR 2721 or with WR 1065, the melting point (T(m)) obeys a Schildkraut-Lifon type equation: T(m) = a log c + b (where c is the concentration of the drug). This interaction is essentially an electrostatic one and involves the cationic groups of WR 2721 or WR 1065 and the anionic phosphate groups of DNA. By dielectric measurement, it is possible to determine the conductivity behavior of these drugs and also their electrostatic interaction with biomolecules. The interaction of WR 2721 and WR 1065 with DPPC smetic mesophases (in vestigated by spectrophotometric and dielectric measurements) is discussed with regard to ionized groups of the phosphatidylcholine polar head and those of the drugs. The theoretical electrostatic properties of these drugs are investigated by using the ab-initio quantum method and by visualization of the electrostatic potential. (5 Refs)

336. RADIOPROTECTORS OF MEA TYPE - AMINOACIDS AND PEPTIDES

Oiry J, Imbach J
Direction des Recherches et Moyens d'Essais, Paris, France
Available from National Technical Information Service, Springfield, VA as NTIS/PB85-117273, 49p 1984

The authors have observed the synthesis of a new class of radio protectors characterized by a pseudopeptidic structure with the objective of succeeding in optimizing this type of drug with structure - activity studies. Among the new derivatives obtained, the I 109 has proven itself one of the most promising. On the other hand, this group of compounds seems to exhibit anticarcinogenic properties, which allows us to contemplate their use as an additional drug in radiation and chemotherapy treatments. (Author abstract)

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337. FLOW CYTOMETRY TECHNIQUES FOR STUDYING CELLULAR THIOLS

Durand RE, Olive PL
Johns Hopkins Oncology Center, Section of Radiobiology, Baltimore, Maryland.
Radiat Res; 95(3):456-70 1983

Cellular thiols, and especially glutathione, act as scavenger nucleophiles and can protect against toxicity, mutagenicity, or transformation by ionizing radiation and many carcinogens. Development of a rapid assay to quantitate the cellular content of thiols could thus be useful in assessing or predicting cellular risk to damage. Several fluorescent thiol-reactive drugs, usually maleimide or bromobimane derivatives, have been described for use in histopathology. Most of these agents do not distinguish between protein and nonprotein thiols, and virtually all of these fluorescent stains have normally been used after fixation of the cells or tissues. We have found that some of the probes will, however, rapidly penetrate and bind within viable cells with little associated cytotoxicity; the amount bound can be easily quantified using flow cytometry. We have used several of these agents, in conjunction with fluorescence-activated cell sorting in V79 spheroids, to examine the thiol content of cells as a function of their depth or position in the spheroid. Additionally, the radiation response of cells from different depths has been assessed following addition of exogenous thiols including glutathione and WR-2721, or after treatment with thiol-depleting agents, including DL-buthionine-S,R-sulfoximine (BSO), diethylmaleate (DEM), and dimethylfumarate (DMF). Our studies indicate that examination of the thiol content and radiation response of the sorted cells provides an improved understanding of the modes of action of these compounds.

338. SYNTHESIS OF AMINOALKYLTHIOPHOSPHORIC ACIDS

Tong Z, Du Y
PLA Acad. Medical Sciences, Beijing, People's Republic of China
Yaoxue Xuebao; 16(4):302-305 1981

In recent yr, promising radiation-protective agents have appeared. The aminoalklythiophosphoric acids, especially S-2-(3-aminopropylamino)ethylthiophosphoric acid [WR-2721], can selectively protect normal tissue from radiation injuries while offering practically no protection for tumor tissues during radiotherapy. An improved method for the synthesis of aminoalkylthiophosphoric acids is described. Numerous aminoalkylthiophosphoric acids where prepared and screened for radiation-protective activities. (8 Refs)

339. MOUSE ENDOGENOUS SPLEEN COUNTS AS A MEANS OF SCREENING FOR ANTI-RADIATION DRUGS

Kinnamon KE, Ketterling LL, Stampfli HF, Grenan MM
Dept. Biology, Walter Reed Army Inst. Res., Washington, D. C., 20012
Proc Soc Exp Biol Med; 164(3):370-373 1980

Eight proven radioprotective compounds were used to compare the standard survival method and a new method employing the counting of macroscopic spleen colonies from mice in assessing the degree of radioprotection. Although both systems were of equal reliability, the new method allowed complete assessment after 10 days instead of the 30 days needed for the standard method. (21 Refs)

340. S-2,OMEGA-DIAMINOALKYL DIHYDROGEN PHOSPHOROTHIOATES AS ANTIRADIATION AGENTS

Piper JR, Ross LM, Johnston TP, Grenan MM
Kettering-Meyer Lab., Southern Res. Inst., Birmingham, AL, 35205
J Med Chem; 22(6):631-639 1979

To enable further structure-activity comparisons among radioprotective phosphorothioates, S-2,omega-diaminoalkyl dihydrogen phosphorothioates were synthesized from L-2,4-diaminobutyric acid, L-ornithine, L-lysine, and DL-2,7-diaminoheptanoic acid as homologues of S-2,3-diaminopropyl dihydrogen phosphorothioate (4) and as isomeric analogues of S-2-[(omega-aminoalkyl)amino]ethyl dihydrogen phosphorothioates (eg, 1). The preferred route that evolved from exploratory trials retained optical activity and involved the reduction of methyl 2,omega-bis(benzoylamino)alkanoates with lithium borohydride, debenzoylation-bromodehydroxylation, and reaction of the resulting 1-(bromomethyl)-1,omega-alkanediamine dihydrobromides with trisodium phosphorothioate. The products of an alternative route that involved the reduction of phthaloylated intermediates with sodium borohydride were racemic. Exploratory conversions of N-(omega-alkenyl)phthalimides failed to provide suitable precursors of the target compounds. In terms of a protective index, these homologues were significantly more radioprotective than the parent phosphorothioate 4 when administered ip to mice prior to whole-body gamma irradiation. The homologues derived from L-lysine also showed good peroral activity. No apparent difference was observed in the protection afforded by optically active homologues and the corresponding racemates. (Author abstract) (42 Refs)

341. SEARCH FOR NEW RADIOPROTECTIVE AGENTS. 41. SYNTHESIS OF SOME UNSYMMETRICAL DISULFIDES AND SULFENAMIDE DERIVATIVES OF QUINOLINE N-OXIDE

Senczuk L, Sobolewski H, Rzemykowska Z
Zaklad Technologii Chemicznej Srodkow Leczniczych, Instytut Chemii i Analityki AM, ul. Grunwaldzka 6, 60-780 Poznan, Poland
Acta Pol Pharm; 36(5):557-560 1979

4-(2'-Nitrophenyl)dithioquinoline N-oxide, 4-(3'-nitrophenyl)-dithioquinoline N-oxide, 4-(4'-nitrophenyl)dithioquinoline N-oxide, 4-(2',4'-dinitrophenyl) dithioquinoline N-oxide, 6-(2'-nitrobenzenesulfenamido)quinoline N-oxide, and 6-(2',4'-dinitrobenzenesulfenamido)quinoline N-oxide were synthesized as potential radioprotective agents. (16 Refs)

VIII.

STRUCTURE - ACTIVITY STUDIES OF RADIOPROTECTORS

342. SYNTHESIS AND METABOLIC MEASUREMENTS OF [13C]-WR3689 (MEETING ABSTRACT)

Krohn KA, Grundbaum Z, Wade RA, Renzoni GE, Rasey JS, Spence AM
Univ. of Washington, Seattle, WA 98195
Thirty-third Annual Meeting of the Radiation Research Society. May 3-9, 1985, Los Angeles, California, p. 98, 1985.

The radioprotective effect of phosphorothioates depends on their concentration and their intracellular chemical form. We have used HPLC of 3H and 35S labeled drugs to separate metabolites by this technique but, due to instantaneous reaction with endogenous thiols, chemical changes caused by sampling and by reaction with the chromatography system,

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HPLC is inadequate. As an alternative chemical assay, we have labeled WR3689 with enriched, stable C-13 at the position adjacent to sulfur. Phosphorothioates undergo a sequence of reactions in vivo: R-S-Phos - - R-SH - - R-S-S-R' - - sulfinates - - sulfonates - - sulfates. We have shown that the NMR chemical shift from the C-13 atom is sensitive to the oxidation state of the sulfur. This technique will allow us to avoid invasive sampling of tissues for analytical chemical measurements and, we believe, will lead to topical NMR spectroscopic mapping of the chemical form of administered [C-13]-phosphorothioates. Data are presented in a table.

343. POLYETHYLENE GLYCOL AS A PROTECTOR AGAINST HEAD AND NECK IRRADIATION

Shaeffer J, Schellenberg KA
Department of Radiation Oncology and Biophysics, Eastern Virginia Medical School, Norfolk.
Int J Radiat Oncol Biol Phys; 10(12):2329-33 1984

Mice injected i.p. with polyethylene glycols (PEG) 20 min prior to head and neck X irradiation with 1650 rad showed improved survival, increased food and water consumption, and retention of body weight compared with irradiated controls. The LD 50/15 for PEG-treated mice was 1900 +/- 108 rad compared to 1527 +/- 56 for the controls. PEG of molecular weights 200, 400, and 600 afforded significant levels of radioprotection; PEG of molecular weights 1000, 1450, 4000, and 20,000 when given at maximum tolerated doses (approximately 0.5 LD 50) did not. The degree of radioprotection by PEG with molecu lar 400 given 20 min before irradiation increased with dose up to the maximum tolerated dose of 6.4 g/Kg. Significant, but lower, levels of radioprotection were observed when the PEG was given 5 min after irradiation. Mice injected i.p. with PEG, cystamine, 5-thioglucose, chlorpromazine, polyethylene glycol monomethyl ether or polyvinylpyrrolidone all had comparable survival levels. Polypropylene glycol, polyethylene glycol diacrylate, and polycaprolactonediol were more toxic than PEG and showed no radioprotection.

344. RADIOPROTECTIVE ACTIVITY OF SOME BETA-HYDROXYLATED INDOLE-ALKYLAMINES

Deanovic Z, Trescec A, Kveder S, Iskric S, Supek Z
Dept. Biology, Rudjer Boskovic Inst., POB 1016, 41 001 Zagreb, Yugoslavia
Strahlentherapie; 158(6):375-377 1982

Chain beta-hydroxylated derivatives of tryptamine, 5-methoxytryptamine and 5-hydroxytryptamine (serotonin), respectively, were tested as radioprotectors in x-ray-irradiated mice. At midlethal dose of irradiation (725 cGy), tryptamine and serotonin protected all the animals, beta-hydroxylated tryptamine was only slightly less effective (survival 85%). On the contrary, when mice were irradiated with absolutely lethal dose (900 cGy), only beta-hydroxylated derivative of serotonin gave complete (100%) protection to the animals; 5-hydroxytryptamine and 5-methoxytryptamine protected about 90% of the animals. Beta-hydroxy-5-methoxytryptamine 35%, tryptamine 29%, whereas beta-hydroxytryptamine did not give any protection. (Author abstract) (10 Refs)

345. SEARCH FOR RADIOPROTECTIVE COMPOUNDS. PART XIX. PROTECTION PROVIDED TO MICE BY ORAL ADMINISTRATION OF LIPID- AND WATER-SOLUBLE COMPOUNDS

Grant GA, Leach KE
Defence Res. Establishment, Ottawa, Ontario, Canada
Search for Radioprotective Compounds. Part XIX. Protection Provided to Mice by Oral Administration of Lipid- and Water-Soluble Compounds. Available from National Technical Information Service, Springfield, VA, as AD-A095 715/9:, 63 pp., 1981.

Forty-two compounds previously screened at the Walter Reed Army Institute of Research were selected for further evaluation. The compounds were administered po to mice prior to gamma irradiation. The LD LD(50/30) was computed and dose reduction factors determined. Dose radiation factors up to 1.45 were obtained for both water- and lipid-soluble compounds with administered oral doses of 100 mg/kg or less. The relationship between chemical structure and protective activity of the compounds is discussed. (Author abstract)

346. RADIOPROTECTIVE AND TOXIC PROPERTIES OF PHENYLETHYLAMINE DERIVATIVES MODIFIED BY ALPHA-AMINO ACIDS

Iliuchenok TIu, Shadurskii KS, Rogozhin SV, Iashunskii VG, Frigidova LM, Butaeva VI, Davidovich IuA
Res. Inst. Medical Radiology, Obninsk, USSR
Radiobiologiia; 22(2):269-275 1982

Toxicity and radioprotective activity of beta-phenylethylamine (b-PEA) derivatives modified by L-lys ine, L-isoleucine, L-methionine, and glycine were studied in female randombred mice. Substitution of hydroxyl in the benzene ring of b-PEA by alkoxy groups resulted in marked increase of toxicity. The highest radioprotective activity was observed in amino acid derivatives of para-pentoxy-, para-methoxy-, and para-heptoxy-derivatives of b-PEA. (8 Refs)

347. TOXICOLOGICAL AND RADIOBIOLOGICAL CHARACTERISTICS OF SOME S-DERIVATIVES OF MEPRIN

Pantev TP, Topalova SP, Isakov IL
Inst. Roentgenology and Radiobiology, Sofia, Bulgaria
Farmakol Toksikol; 44(4):476-478 1981

Toxicity and radioprotective activity of four derivatives of alpha-mercaptopropionylglycine (MPG) were studied in mice (strain unspecified). Thiosulfate and thiophosphate derivatives of MPG provided a 63-90% survival of irradiated animals (900-950 rads); both derivatives had low toxicity. Isothiuronium derivative failed to provide a radioprotection, while diethyldithiocarbamate derivative had low radioprotective activity. (9 Refs)

348. RADIOPROTECTIVE CHARACTERISTICS OF OPTICAL ISOMERS OF DEHYDROBROMIDE S-(2-AMINOPENTYL)ISOTHIOUREA IN MAMMALS AND CELLS IN VITRO

Gratvskii EYa, Ianushevskaia MI, Mandrugin AA, Nekrasova IV, Bueverova EI, Bragina EV, Khomutov SM, Fedoseev VM
N. K. Kol'tsov Inst. Developmental Biology, USSR Acad. Sciences, Moscow, USSR
Radiobiologiia; 20(5):752-757 1980

A comparative study of radioprotective activities of D-, L-forms and the racemate dehydrobromide S-(2-aminopentyl)isothiourea (DU) was conducted in gamma-irradiated hybrid mice, x-irradiated Ehrlich ascitic carcinoma (EAC) cells, and x-irradiated Chinese hamster fibroblasts in vitro. In experiments on mice, it was found that only the racemate DU displayed a tendency towards increasing radiore-

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sistance of mice (based on survival and median life span indices), whereas D- and L-forms had no effect at all. Studies in the EAC cells and Chinese hamster fibroblasts showed that DU and its isomers can produce equally effective radioprotective effects. It was concluded that the radioprotective action of DU on the isolated cells is similar to that of other 2-aminoethylisothiouronium bromide hydrobromide analogs. (12 Refs)

349. 1-HETERYLPYRAZOLES AND THEIR RADIOPROTECTIVE CHARACTERISTICS

Novikova AL, Postovskii II, Puchkova SM, Chechulina LA, Tuzhilkova TN
S. M. Kirov Ural'skii Polytechnical Inst., Sverdlovsk, USSR
Khim Farm Zh; 14(6):46-49 1980

The following 3,5-dialkylpyrazoles, containing thiazole and benzothiazole rings in position 1, were synthesized: 1-(4'-methylthiazolyl-2')-3,5-dimethylpyrazole (I), 1-(4'-phenylthiazolyl-2')-3,5-dimethylpyrazole (II), 1-[4'-(3', 4'-dioxyphenyl)-thiazolyl-2]-3,5-dimethylpyrazole (III), and 1-[4'-(3',47-dioxyphenyl)-thiazolyl-2]-3-methyl-5-tetrafluoro-ethylpyrazole (IV). The effects of benzothiazolyl (V) were compared to those of benzimidazolyl (VI). Experiments were conducted on 400 male C57BL/6 mice, which were ip injected with 0.2 ml each of the tested compounds dissolved in peach oil. All animals were gamma-irradiated with 950 R. Comparisons of the toxic doses of the compounds tested showed that their LD50s varied from 250 (compound IV) to 3,000 mg/kg (II and V), ie they all have low toxicity. Radioprotective characteristics were found in two of the compounds (II and VI); both increased the survival of animals by 50-60%, relative to the control. The study of pharmacological activity of compound VI showed that it reduces oxygen absorption and body temperature in animals. (6 Refs)

350. SYNTHESIS AND RADIOPHARMACOLOGICAL STUDY OF UNSATURATED CYSTEAMINE DERIVATIVES

Mesnard D, Miginiac L, Fatome M, Laval JD, Sentenac-Roumanou H, Lion C
Laboratoire de Synthese organique, Universite de Poitiers, 40, avenue du Recteur Pineau, 86022 Poitiers, France
Eur J Med Chem; 15(3):247-252 1980

Synthesis of many unsaturated compounds derived from cysteamine, one of the best known radioprotector agents, has been carried out in the three series: beta-aminothioethers (I), beta-aminothiols (II) and thioazolidines (III). These products are more or less toxic compared to corresponding saturated derivatives. They generally have a higher radioprotective activity when administered ip in mice at half the LD50 dose, 15 min prior to irradiation. The three most effective are propargylic beta-aminothiol (II) and two ethylenethioazolidines (III); they have a dose reduction factor (ie, ratio of the LD50/30 days of protected animals to the LD50 of unprotected) similar to that of cysteamine (1.5). The two ethylenethioazolidines are less toxic than cysteamine. (22 Refs)

351. SYNTHESIS AND RADIOPROTECTIVE ACTIVITY OF DERIVATIVES OF ACETAMIDINTHIOPHOSPHOROUS ACID

Tilov BA, Zherebchenko PG, Krasheninnikova EA, Kostun VI, Terekhov AV, Znamenskii VV, Kalistratov GV, Iashunskii VG
Inst. Biophysics, Moscow, USSR
Khim Farm Zh; 13(11):26-31 1979

The radioprotective activity of a series of newly synthesized derivatives of 2-acetamidinthiophosphorous acid was tested in CBA x C57BL mice. The ip or po administration of C-alkyl-substituted 2-acetamidinthiophosphorous acid increased the survival rate of irradiated (950 R) animals. Introduction of a methyl group into the alpha-C atom did not change the toxicity of compounds and protective activity at ip administration, but caused a 1.5 x decrease in the toxicity and an approx 1.5 x increase in the radioprotective activity at po administration. Further elongation of the hydrocarbon chain (introduction of propyl and especially octyl group) caused a marked increase in the toxicity and decrease in the radioprotective activity. (6 Refs)

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IX.

THE USE OF RADIOPROTECTORS IN MODIFYING THE TOXIC SIDE EFFECTS OF CHEMOTHERAPEUTIC AGENTS

A.

Alkylating Agents

1.

Human Studies

352. WR-2721 PROTECTS AGAINST THE HEMATOLOGIC TOXICITY OF CYCLOPHOSPHAMIDE: A CONTROLLED PHASE II TRIAL

Glover D, Glick JH, Weiler C, Hurowitz S, Kligerman MM
Department of Medicine, University of Pennsylvania, Philadelphia.
J Clin Oncol; 4(4):584-8 1986

WR-2721 S-2-(3-aminopropylamino) ethyl phosphorothioic acid, is an organic thiophosphate compound that in the animal model selectively protects against the hematologic toxicity of cyclophosphamide by factors of 1.5 to 2.0. Preliminary data from our controlled phase I trial of WR-2721 and cyclophosphamide suggested that WR-2721 protected against cyclophosphamide-induced granulocytopenia. Since variable drug doses and infusion rates were used in these early studies, we initiated a controlled phase II trial using constant drug doses to establish more precisely WR-2721's level of protection. Initially, 21 patients received 1,500 mg/m2 of cyclophosphamide alone and were retreated 4 weeks later after hematologic recovery was complete with 740 mg/m2 of WR-2721 before the same dose of cyclophosphamide. With WR-2721 pretreatment, 19 of 21 (90%) patients had improved WBC and granulocyte counts. The mean WBC increased from 1,760/mL with cyclophosphamide alone to 2,500/mL with WR-2721 pretreatment (P less than .0005). The mean granulocyte count increased from 541/mL on cyclophosphamide to 1,247/mL with WR-2721 and cyclophosphamide (P less than .0005). Following cyclophosphamide administration alone, neutropenic fevers developed in three patients. No patient experienced a febrile episode following WR-2721 and cyclophosphamide administration. Platelet nadirs below 100,000/mL were only noted in two patients treated with cyclophosphamide alone. Objective partial responses were observed in four of 19 (21%) patients with measurable or evaluable disease. These data suggest that WR-2721 provides significant protection against cyclophosphamide-induced hematologic toxicity.

353. WR-2721 PROTECTS AGAINST THE HEMATOLOGIC TOXICITY OF CYCLOPHOSPHAMIDE

Phillips TL
University of California, San Francisco.
J Clin Oncol; 4(4):458 1986

Keywords (MeSH): Bone Marrow/*drug effects; Cyclophosphamide/*toxicity; Ethiofos/*therapeutic use; Human; Neo-

plasms/drug therapy; Organothiophosphorus Compounds/ *therapeutic use.

354. WR-2721 PROTECTS AGAINST THE HEMATOLOGIC TOXICITY OF CYCLOPHOSPHAMIDE: A CONTROLLED PHASE II TRIAL (MEETING ABSTRACT)

Glover D, Glick J, Weiler C, Kligerman M
Hematology-Oncology Section, Cancer Center, Univ. of Pennsylvania, PA 19104
Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-28, 1985.

In the animal model WR-2721 selectively protects against the hematologic toxicity of cyclophosphamide (CYC) by factors of 1.5 to 2.0. Using WR-2721 doses (450-1100 mg/m2) and CYC doses (1200-1800 mg/m2), we have previously reported that 23/40 (58%) patients (pts) had improved WBC nadirs with WR 2721 pretreatment compared to WBC nadirs with the same dose of CYC alone. Since variable CYC and WR-2721 doses and infusion rates were used in these early Phase I trials, we initiated a controlled Phase II study using constant drug doses to establish more precisely WR-2721's level of protection. Initially 21 pts received 1500 mg/m2 of CYC alone over 1 hr, and were retreated 4 wk later after hematologic recovery was complete with 740 mg/m2 of WR-2721 prior to the same dose of CYC. Thus, each pt serves as his own control. WR-2721 was given over 15 min. CYC was given over 1 hr beginning 15 min after the WR-2721 infusion was complete. Hematologic profiles and granulocyte counts (GRC) were obtained 3 times a wk until hematologic recovery was complete. There were 11 men and 10 women with a median age of 58 yr (range 49-72). Three pts had received prior chemotherapy, 3 pts prior radiotherapy and 3 pts both prior chemotherapy and radiotherapy. All pts had histologically confirmed metastatic malignancies, for which no conventional chemotherapy or radiotherapy offered significant palliation. With WR-2721 pretreatment, 19/21 (90%) pts had improved WBC counts. The mean WBC increased from 1760/mm3 on CYC alone to 2500/mm3 with WR-2721 and CYC (p = less than 0.0005). Improved GRC were noted in 19/21 (90%) pts with WR-2721. The mean GRC count increased from 541/mm3 on CYC to 1247/mm3 with WR-2721 and CYC (p = less than 0.0005). Platelet nadirs below 100,000/mm3 were only noted in 2 pts treated with CYC alone. No pt had thrombocytopenia with WR-2721 and CYC. Following CYC alone, 2 pts devcloped fever with granulocytopenia. No pt developed an infection following WR-2721 and CYC. The data presented in a table suggest that 740 mg/m2 WR-2721 provides significant protection against CYC-induced granulocytopenia. Future studies will include controlled trials of CYC with multiple divided doses of WR-2721, to determine whether the level of protection increases when WR-2721 is given prior to and 3 and 6 hr after CYC.

355. WR2721 PROTECTS NERVES FROM CIS-PLATINUM TOXICITY (MEETING ABSTRACT)

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Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-30, 1985.

The neuropathy associated with cis-diaminedichloroplatinum II (DDP) is currently the most frequent dose-limiting side effect experienced by patients (pts) at the University of Pennsylvania. We began a prospective study of pts receiving DDP to assess the effectiveness of WR2721, a chemo-protective agent, in preventing the development of neuropathy. Pts receiving cis-platinum were evaluated by a single neurologist prior to beginning therapy and periodically throughout their course. Fifty-six pts were distributed among the following protocols: DDP 50 mg/m2, doxorubicin 50 mg/m2, cyclophosphamide 500 mg/m2 monthly for 9 mo (19); DDP 120 mg/m2 + vinblastine 1.6 mg/m2/day X 5 every 3 wk (8); DDP 40 mg/m2/day X 5 + cyclophosphamide 1.5 gm/m2 monthly (7); DDP 80-150 mg/m2 + WR2721 740 mg/m2 monthly (19); DDP 120 mg/m2 monthly; Misc - DDP 20 mg/m2/day X 5 + vinblastine 0.2 mg/kg/day X 5 + VP16 100 mg/m2 day X 5 + bleomycin 30 U alternating monthly with cyclophosphamide, methotrexate and actinomycin D (1). Dose of DDP at onset of neuropathy was defined as that dose at which the pts first complained of symptoms of neuropathy or at which the examiner noted a decrease in sensation or reflexes relative to the baseline exam, whichever dose was lower. The character of the neuropathy was the same as that which has been described previously. Reflexes and vibratory sensation were diminished early and often before pts complained of symptoms. Initial symptoms included paresthesias and/or numbness. Pts with more severe neuropathies had a marked sensory ataxia due to loss of joint position sensation. Overall, neuropathy occurred in 48% of pts at a mean total dose of 399 mg/m2. Pts receiving DDP + WR2721 had a significantly lower incidence of neuropathy of 26% (p less than 0.05), and the onset occurred at a significantly higher cumulative dose of 670 mg/m2 (p less than 0.01). We conclude that WR2721 may protect nerves as well as kidneys from DDP toxicity.

356. LIMITATION OF CIS-PLATINUM OTOTOXICITY BY A PROTECTOR AGENT, WR-2721 (MEETING ABSTRACT)

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Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-29, 1985.

A new protector agent, WR-2721 (S-2-(3-aminopropylamino) ethyl phosphorothioic acid) is under investigation because of its ability to protect normal tissues from the effects of ionizing radiation and radiomimetic anti-neoplastic drugs. Sixteen cancer pts treated with high dose cis-platinum (120-150 mg/M2) who were pretreated with the protector drug WR-2721 (740 mg/M2) were studied prospectively for evidence of ototoxicity. Pure tone thresholds were obtained at eight frequencies from 250 Hz to 8 KHz, prior to initiation of therapy, and after each cycle of chemotherapy. After the first course of treatment, mean thresholds were stable (0-5dB shift) from 250 Hz - 2 KHz, there was a mean shift of 10dB at 3 and 4 KHz, 15dB at 6 KHz, and 20dB at 8 KHz. Subsequent courses of cis-platinum and WR-2721 resulted in additional sensitivity loss in a similar pattern, with the greatest mean decrease after three cycles of therapy being 25dB at 8 KHz. The magnitude of sensitivity loss encountered in this group of patients compares favorably with that reported in pts receiving lower doses of cis-platinum (100 mg/M2 or less) alone. WR-2721 appears to increase the therapeutic index of cis-platinum with reference to ototoxicity, and deserves additional study in clinical trials.

357. CIS-PLATIN NEUROPATHY: A POSSIBLE PROTECTIVE AGENT (MEETING ABSTRACT)

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Proc Am Soc Clin Oncol; 4:34 1985

The neuropathy associated with cis-diaminedichloroplatinum II (DDP) is currently the most frequent dose-limiting side effect experienced by patients at the University of Pennsylvania. We began a prospective study of patients receiving DDP to determine what factors were associated with the develop-

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ment of neuropathy and to assess the effectiveness of WR2721, a chemoprotective agent, in preventing it. Patients receiving five different drug regimens were assessed: DDP alone (4); DDP, doxorubicin, cyclophosphamide (18); high dose DDP (40 mg/m2 x 5 days), cyclophosphamide (2); DDP, vinblastine (4); and DDP, WR2721 (14). Overall, neuropathy occurred in 31% of patients at a mean total dose of 395 mg/m2. There was no correlation with age, sex, personal or family history of diabetes, alcohol consumption, smoking, or previous chemotherapy. (Patients with preexisting neuropathy from vincristine exposure were excluded.) None of the patients had a history of exposure to industrial neurotoxins or family history of hereditary neuropathy. Only 21% of patients receiving DDP and WR2721 developed neuropathy at a significantly higher mean total dose of 763 mg/m2 (p less than 0.001). Both of the patients who received high dose DDP and cyclophosphamide developed neuropathy after the first or second course of therapy (mean total dose of 300 mg/m2) requiring that DDP be eliminated from later courses. We conclude that WR2721 may be chemoprotective for nerves as well as bone marrow and kidneys. Also, dose of DDP/time may be a factor in the development of neuropathy, although more patients need to be studied.

358. PHASE II CLINICAL TRIAL OF WR-2721 AND CIS-PLATINUM (DDP) IN ADVANCED MALIGNANT MELANOMA (MEETING ABSTRACT)

Glover D, Weiler C, Guerry D, Fox K, Glick J
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Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-27, 1985.

Phase II trial of WR-2721 and cis-platinum (DDP) was conducted. Patients (pts) received 740 mg/m2 of WR-2721 over 15 min. Beginning 15 min after the WR-2721 infusion was complete, pts received 80-150 mg/m2 of DDP over 30 min. Treatment cycles were repeated every 21 to 28 days. Twenty-four pts have been entered on study. Nineteen were evaluable and 5 were recently entered. Of the evaluable pts there were 14 men and 5 women with a median age of 45 yr (range 25-70). Thirteen pts had received prior chemotherapy, 5 had prior radiotherapy. All pts had well documented progressive disease prior to tre atment. Objective partial responses (PR) were observed in 11 of 19 pts (58%) with metastatic melanoma treated with the combination of WR-2721 (740 mg/m2), DDP, and mannitol diuresis. Two additional pts had minor responses. The median duration of response was 6 mo (range 1+-9 mo). Partial responses occurred in 6/11 pts with prior chemotherapy. The sites of responding metastases were skin and sc sites (9/13 pts), nodes (7/10 pts), liver (3/7 pts), and lung (1/4 pts). The median survival was 7 mo (range 1-15+ mo) for all pts and 11+ mo (range 3-15+) for partial responders. Transient nephrotoxicity was observed in 7 of 81 courses of DDP. Platelet counts below 100,000/mm3 were noted in 11/81 courses. Granulocyte counts less than 1500/mm3 were observed in 9/81 courses. Seven pts developed peripheral neuropathy following 460-1060 mg/m2 of DDP. Ten pts experienced clinical hearing loss. Preliminary data suggest that WR-2721 may potentiate the anti-tumor activity of DDP in melanoma.

359. PHASE I/II TRIALS OF WR-2721 AND CIS-PLATINUM (DDP) (MEETING ABSTRACT)

Glover D, Glick J, Weiler C, Fox K, Turrisi A, Kligerman M
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Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-25, 1985.

The dose limiting toxicity of cis-platinum (DDP) is nephrotoxicity. Al Sarraf, et al (Cancer Treat Rep 66:31-35, 1982) reported a 32% incidence of nephrotoxicity after 100 mg/m2 of DDP with hydration and mannitol diuresis. Without mannitol they reported a 39% incidence of renal toxicity. WR-2721 (WR) is a sulfhydryl compound which in the animal model improves renal tolerance to DDP by factors of 1.3 to 1.7. Phase I trials were initiated to establish the toxicity when WR was given prior to escalating doses of DDP. Nineteen patients (pts) received 27 courses of WR (450-910 mg/m2) at 15 mg/m2/min prior to 50-120 mg/m2 of DDP. Pts were prehydrated, but mannitol or diuretics were not given. Mild, transient nephrotoxicity was observed in only 2/15 courses of DDP 80-100 mg/m2. 5/9 pts treated with WR and 120 mg/m2 DDP developed transient nephrotoxicity. Subsequently the protocol was modified to include mannitol diuresis. As shown in table, 40 pts received 125 courses of WR prior to DDP (80-150 mg/m2) with mannitol and hydration. Nephrotoxicity, measured by biweekly serum creatinines and in many cases monthly creatinine clearances, occurred in only 5/78 (6%) courses with 120 mg/m2 of DDP. With 150 mg/m2 of DDP, 6/17 (35%) courses were associated with transient nephrotoxicity. Five pts who experienced nephrotoxicity after 150 mg/m2 of DDP were subsequently retreated with WR and DDP 100 mg/m2 without nephrotoxicity. Twelve pts received 30 courses of WR-2721 and reduced DDP doses (60-100 mg/m2) (2 because of pre-existing renal dysfunction and 10 because of hematologic, oto-, or neurotoxicity). No pt with normal renal function prior to DDP had permanent nephrotoxicity. Data are presented in a table. In both trials objective partial responses were observed in 29/57 (49%) pts. Six of 19 pts (32%) treated without mannitol and 23/38 (61%) pts treated with mannitol had partial responses. Summary: At the conventional DDP dose of 120 mg/m2 and WR only 6% of our pt courses were associated with transient nephrotoxicity. However, we were unable to consistently escalate DDP doses to 150 mg/m2 because of transient nephrotoxicity. Compared to retrospective series our data suggest that WR may provide some protection against DDP-induced nephrotoxicity. Controlled trials will be required to define the potential clinical benefit of WR and DDP. (1 Ref)

360. PHASE II CLINICAL TRIAL OF WR-2721 AND CIS-PLATINUM (DDP) IN METASTATIC CARCINOMA OF THE HEAD AND NECK (MEETING ABSTRACT)

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Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-26, 1985.

With monthly doses of DDP 100 mg/m2 alone, objective responses are observed in 25-39% of patients (pts) with advanced head and neck cancer (HNC). During the course of our Phase I trials of WR-2721 and DDP, objective partial responses (PR) were noted in pts with HNC. These observations led to a larger Phase II trial of WR-2721 and DDP to define the PR rate of this regimen in pts with metastatic or locally recurrent HNC. All pts were prehydrated for at least 12 hr prior to DDP. DDP was given over 30 min, beginning 15 min after the WR-2721 infusion was complete. Initially, WR-2721 (450-910 mg/m2) was given at a rate of 15 mg/m2/

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min without mannitol diuresis. Subsequently pts received 740mg/m2 of WR-2721 over 15 min and DDP was given with standard mannitol diuresis. There were 11 men and 5 women with a median age of 61 (range 42 to 72). 15/16 pts had prior radiotherapy and 4/16 prior chemotherapy. No pt had prior DDP. Overall, 9/16 (56%) pts had objective PR's. PR's occurred in 3/7 pts treated with WR-2721 and DDP (50-120 mg/m2) without mannitol and 6/9 pts treated with WR-2271, DDP (100-150 mg/m2), and mannitol diuresis. The sites of responding metastases included: sc tissue (2/4 pts); lymph nodes (7/10 pts); lung (3/5 pts); and primary tumor (6/6 pts). The duration of response ranged from 4 to 24+ wk. The median survival for all pts was 7 mo. Transient nephrotoxicity occurred in 1 pt treated with WR-2721 + DDP 120 mg/m2 without mannitol diuresis and in 2 pts after 150 mg/m2 of DDP with mannitol and WR-2721. Platelets less than or equal to 100,000/mm3 and granulocytes less than or equal to 1500/mm3 were noted in 4/35 and 14/35 courses, respectively. Two pts experienced clinical hearing loss. No pt developed alopecia or neurotoxicity. These data suggest that WR-2721 may potentiate the anti-tumor efficacy of DDP in HNC, but controlled clinical trials will be initiated to determine the degree of clinical benefit. A Phase II trial of WR-2721, DDP, and radiotherapy will also be initiated for pts with unresectable Stage III and IV HNC.

361. PHASE I TRIALS OF WR-2721 AND CIS-PLATINUM

Glover D, Glick JH, Weiler C, Yuhas J, Kligerman MM
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Int J Radiat Oncol Biol Phys; 10(9):1781-4 1984

WR-2721 is a sulfhydryl compound which in the animal model improves renal tolerance to cis-platinum (DDP) by factors of 1.3 to 1.7. Phase I trials were initiated to establish the toxicity and dose modification factors when WR-2721 was given prior to escalating doses of DDP. Nineteen patients received 27 courses of WR-2721 (450-910 mg/m2) 20 minutes prior to DDP (50-120 mg/m2). Patients were prehydrated, but no mannitol or other diuretics were administered. Mild, transient nephrotoxicity was observed in only 2 of 15 courses of DDP 80-100 mg/m2 when WR-2721 was given prior to DDP. Although 5 of 9 patients treated with WR-2721 prior to 120 mg/m2 of DDP developed transient nephrotoxicity, their serum creatinines returned to normal baseline values within 1 to 2 weeks. Subsequently, the protocol was modified to include mannitol diuresis. Thirty-four courses of WR-2721 (740 mg/m2) prior to DDP 120-150 mg/m2 with mannitol diuresis were administered. Biweekly serum creatinine and monthly creatinine clearances have remained normal in all patients treated with 120 mg/m2 of platinum and WR-2721. Four of 10 patients treated with 150 mg/m2 of cis-platinum experienced transient nephrotoxicity 5-7 days after treatment. Mild ototoxicity was noted in 4 patients following 150 mg/m2 of DDP. WR-2721 does not appear to protect against the antitumor efficacy of DDP, as 57% of all patients achieved objective partial responses, lasting 1+ to 7+ months. Partial responses occurred in 3/4 (75%) of patients with melanoma and 7/10 (70%) patients with cancer of the head and neck. Compared to retrospective series, our data suggest that WR-2721 may provide some protection against platinum-induced nephrotoxicity, but the dose modification factors remain to be established.

362. PHASE I CONTROLLED TRIALS OF WR-2721 AND CYCLOPHOSPHAMIDE

Glick JH, Glover D, Weiler C, Norfleet L, Yuhas J, Kligerman MM
Hematology-Oncology Section, Cancer Center, University of Pennsylvania, Philadelphia.
Int J Radiat Oncol Biol Phys; 10(9):1777-80 1984

WR-2721 is an organic thiophosphate compound which in the animal model selectively protects against the hematologic toxicity of cyclophosphamide by factors of 1.5 to 2.0. Controlled Phase I trials of WR-2721 and cyclophosphamide were initiated to determine if WR-2721 protected against cyclophosphamide's hematologic toxicity. Fifteen patients received WR-2721 (450-1100 mg/m2) prior to cyclophosphamide (1200-1800 mg/m2) and were subsequently retreated 4 weeks later with the same cyclophosphamide dose alone. With WR-2721 pretreatment, 11/15 (73%) patients had improved WBC counts. The mean WBC increased from 1800/mm3 on cyclophosphamide alone to 2700/mm3 with WR-2721 + cyclophosphamide ($p = 0.008$). In 11 patients who had nadir differential counts performed, 7 (64%) demonstrated improved nadir granulocyte counts with WR-2721. The mean granulocyte count increased from 765/mm3 on cyclophosphamide to 1274/mm3 with WR-2721 + cyclophosphamide ($p = 0.05$). In the second trial, 25 patients received the reverse sequence: an initial dose of cyclophosphamide (1200-1800 mg/m2) alone, followed 4 weeks later by WR-2721 (450-1100 mg/m2) prior to the same dose of cyclophosphamide. With WR-2721 pretreatment, 12/25 (48%) patients had improved nadir WBC counts. The mean WBC increased from 1550/mm3 on cyclophosphamide alone to 1850/mm3 with WR-2721 + cyclophosphamide ($p = 0.02$), while the nadir granulocyte count increased from 449/mm3 to 844/mm3 ($p = 0.001$). No patient developed microscopic or gross hematuria or inappropriate antidiuretic hormone secretion. One patient developed mild thrombocytopenia. These data suggest that WR-2721 provides significant protection against cyclophosphamide-induced granulocytopenia, but the dose modification factors and degree of clinical benefit remain to be established. The current recommended WR-2721 dose for Phase II trials is 740 mg/m2 administered over 15 minutes.

363. CLINICAL TRIAL OF THE EFFECT OF S-2-(3-AMINOPROPYLAMINO)-ETHYLPHOSPHOROTHIOIC ACID (WR-2721) (NSC 296961) ON THE TOXICITY OF CYCLOPHOSPHAMIDE

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J Clin Oncol; 1(3):198-203 1983

S-2-(3-Aminopropylamino)-ethylphosphorothioic acid (WR-2721) is reported to protect normal tissues from the effects of ionizing radiation and possibly alkylating agents as well. The present trial assessed the ability of this compound to modify the clinical toxicity of cyclophosphamide. Patients with advanced cancer first received a dose of 1000 mg/m2 cyclophosphamide intravenously and were observed for toxicity, principally myelosuppression. After the nadir in white blood cell counts and/or platelets had been documented and adequate recovery had occurred, a second course of cyclophosphamide was given, this time preceded by WR-2721 30 min earlier. In this fashion, each patient served as his own control. Doses of WR-2721 ranging from 250 to 1000 mg/m2 were tested. A total of 13 evaluable courses of WR-2721 were given with cyclophosphamide. In no instance did the prior administration of WR-2721 diminish the bone marrow toxicity of cyclophosphamide alone. At the end of the trial two

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additi onal patients received the WR-2721 in a split dose, one-half prior to the cyclophosphamide and one-half 6 hr later; again there was no protection. The side effects of WR-2721 included nausea, vomiting, hypotension, sneezing, and swelling of the tongue. We conclude that WR-2721 is a potentially toxic compound that produces no amelioration of cyclophosphamide toxicity in the doses used. Because of the severity of the side effects of WR-2721, principally hypotension, the trial was terminated after 1000 mg/m2 WR-2721 failed to protect against the toxicity of 1000 mg/m2 cyclophosphamide.

364. PHASE I CLINICAL TRIALS OF WR-2721 WITH ALKYLATING AGENT CHEMOTHERAPY

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Int J Radiat Oncol Biol Phys; 8(3/4):575-580 1982

Preliminary results are presented of three parallel Phase I trials in which WR-2721 was administered prior to escalating single doses of either cis-platinum (DDP), cyclophosphamide (CY), or nitrogen mustard (HN2) in patients with various metastatic or locally recurrent tumors. Doses of WR-2721 ranged from 450-740 mg/square meter (m2) administered as a continuous iv infusion over 20-50 min. Pre- and postchemotherapy hydration were used, the former with CY and DDP, the latter with all agents. Ten patients received 19 courses of CY after 450 mg/m2 WR-2721; moderate leukopenia was noted with a median WBC nadir of 1,800/cubic mm on day 20 at the 1,800 mg/m2 iv dose level of CY. Thirteen patients received 22 courses of DDP after 450-740 mg/m2 WR-2721; transient nephrotoxicity was noted in five courses at DDP doses of 80-120 mg/m2. Moderate leukopenia was observed with 10-16 mg/m2 HN2 after 450-750 mg/m2 WR-2721. Objective partial remission of measurable tumor was observed in 4/12 patients receiving DDP (2 with squamous cell carcinoma of the head and neck, and 1 each with adenocarcinoma of unknown origin and carcinoid). Minor responses were noted in three patients given DDP, two given CY, and one given HN2. While WR-2721 may provide normal tissue protection when administered prior to CY or HN2, the level of protection is not yet of clinical benefit and dose modification factors must be established. However, evidence of bone marrow protection with WR-2721 was obtained from patients treated with CY plus WR-2721 then CY alone. (11 Refs)

365. METHODS OF REDUCTION OF CISPLATIN NEPHROTOXICITY

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Ann Clin Lab Sci; 11(5):397-410 1981

A review is presented of the pharmacology, toxicology, pharmacokinetics, nephrotoxicity, and reduction of toxicity of cisplatin, a platinum-containing compound that is effective against a number of animal tumor systems. The hypothesis explaining the nephrotoxicity of cisplatin states that: (1) it is a direct tubular toxicant, (2) it must be present in tubular urine at a min concentration of approx 1 mM for a given period of time (several hr) for irreversible damage to occur, and (3) its mechanism of toxicity probably is mediated via inhibition of (primarily) the Na, K-ATPase. Numerous treatments and substance have been examined for their ability to reduce cisplatin nephrotoxicity; these include hydration, diuresis, penicillamine, probenecid, superoxide dismutase, WR-2721, diethyldithiocarbamate, thiourea, thiosulfate, and other adjuncts, with favorable results in many cases. There are also platinum derivatives other than cisplatin that have equal or superior therapeutic potential and exhibit less nephrotoxicity. The possible role of prostaglandins in the reduction of cisplatin-induced nephrotoxicity is also discussed. (99 Refs)

2. Experimental Systems

366. PROTECTION AGAINST CIS-DIAMMINEDICHLOROPLATINUM CYTOTOXICITY AND MUTAGENICITY IN V79 CELLS BY 2-[(AMINOPROPYL)AMINO]ETHANETHIOL

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Cancer Res; 46(3):1132-5 1986

The effect(s) of the radioprotector 2-[(aminopropyl)amino]ethanethiol (WR1065) on cis-diamminedichloroplatinum(II) (cis-DDP)-induced cytotoxicity and mutagenesis at the hypoxanthineguanine phosphoribosyl transferase locus in V79 Chinese hamster cells was examined. With a standard exposure time of 30 min for both agents, WR1065, at a final working concentration of 4mM, was added to cells either prior to, during, or immediately following treatment with selected doses of cis-DDP. With respect to cell survival, dose modification factors of 2.9, 1.4, and 1.4 were obtained for cells treated under each of these conditions, respectively. The induction of mutants under all conditions was linear as a function of cis-DDP concentration. Mutation frequencies per microgram of cis-DDP were 25 X 10(-7), 1 X 10(-7), 5 X 10(-7), and 11 X 10(-7) for protocols involving no protector present or WR1065 added before, during, or after cis-DDP treatment, respectively. No WR1065-mediated cytotoxicity to cells derived from either wild-type or mutant colonies was observed. These data demonstrate that WR1065, the free thiol of S-2-(3-aminopropylamino)ethyl phosphorothioic acid (WR2721) which is currently being evaluated in clinical trials, affords substantial protection against the cytotoxic and mutagenic effects of cis-DDP, with the most effective protection occurring when the protector is administered prior to cis-DDP treatment. Due to their ability to better protect normal as compared to tumor tissue against acute effects, these protectors have generated considerable interest for use in improving the therapeutic gain of radiation therapy and chemotherapy. The ability of these compounds to also pr otect against the mutagenic effects of therapy agents may be an important additional benefit for consideration in their use in the treatment of human neoplasia.

367. EFFECT OF THE RADIOPROTECTOR WR 2721 ON THE RESPONSE OF METASTATIC LEWIS LUNG CARCINOMA COLONIES TO ALKYLATING AGENTS

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Acta Radiol kOncoll; 24(3):259-62 1985

WR 2721 protected 'artificial' lung metastases of Lewis lung carcinoma against the cytotoxic effects of cyclophosphamide and melphalan. When mice were pretreated with WR 2721 30 min before exposure to the alkylating agents a significant increase in the number of lung metastases could be observed. This protection of micrometastases had a significant impact on survival in the case of cyclophosphamide treatment, but not in the case of melphalan treatment. The degree of protection at a standard dose of WR 2721 was dose dependent.

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368. PROTECTIVE EFFECTS OF 2-[(AMINOPROPYL) AMINO] ETHANETHIOL AGAINST BLEOMYCIN, NITROGEN MUSTARD, CIS-DIAMMINEDICHLOROPLATINUM, AND RADIATION INDUCED MUTAGENICITY IN V-79 CELLS (MEETING ABSTRACT)

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Chemical Modifiers of Cancer Treatment. October 20-24, 1985, Clearwater, Florida, abstract 7-10, 1985.

The compound 2-[(aminoprophyl) amino] ethanethiol (WR-1065) was investigated with respect to its antimutagenic properties. The effects of WR-1065 as a protector against bleomycin (BLM)-, nitrogen mustard (HN2)-, cis-dichloroammineplatinum (cis-DDP)-, and radiation (XRT)-induced mutagenesis at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus in V-79 Chinese hamster cells were characterized. The radioprotector WR-1065, always made up as a 1M solution in phosphate buffered saline (Dulbeccios PBS:GIBCO), was added to cell cultures 30 min prior to exposure of the cells to the selected chemotherapeutic agents of radiation. The exposure time for all chemotherapeutic agents tested was 30 min. WR-1065 was effective in protecting against cytotoxicity induced by each of the agents tested. Mutation frequencies were determined with a 6-day expression time. The induction of mutants by either BLM, HN2, cis-DDP or XRT, corrected for spontaneous background mutation frequency, was linear in all cases. Mutation frequencies per unit of agent tested were 78.2 x 10(-6) per unit BLM; 66 x 10(-7) per ug HN2; 25 x 10(-7) per ug cis-DDP; and 87 x 10(-7) per Gy of XRT. WR-1065 effectively reduced mutation induction by each of the agents tested to 37 x 10(-6) per unit BLM; 40.6 x 10(-7) per ug HN2; 1 x 10(-7) per ug cis-DDP; and 43.8 x 10(-7) per Gy of XRT. Mutation protection factors (MPF) were determined to be: BLM, MPF = 2.8; HN2, MPF = 3.4; cis-DDP, MPF = 7.1; and XRT, MPF = 5.1. WR-1065 did not of itself induce single-strand breaks (SSB) in control cells following exposure times of up to 180 min. If present during BLM, HN2, or XRT treatment, WR-1065 protected against the formation of SSB.

369. RADIO- AND CHEMOPROTECTION AS A MEANS OF INCREASING THERAPEUTIC RATIO IN THE TREATMENT OF TUMOUR AND ITS METASTASES (MEETING ABSTRACT)

Milas L, Hunter N, Ito H, Peters LJ
Div. of Radiotherapy, M. D. Anderson Hosp. and Tumor Inst., Houston, TX 77030
Treatment of Metastasis: Problems and Prospects. Abstracts of papers presented at a conference held at Strand Palace Hotel, London, October 15-17 1984. Hellmann K, Eccles SA, eds. London, Taylor and Francis, paper 3.7, 1984.

Since normal tissue damage limits therapy of primary tumors and their metastases with cytotoxic agents, selective, or preferential normal tissue protection should increase the therapeutic ratio. Experiments presented here show that this can be achieved in certain circumstances with a free-radical scavenger diethyldithiocarbamate (DDC). The experiments were performed with C3Hf/Kam mice and two syngeneic fibrosarcomas, designated FSA and NFSA. DDC was administered ip at doses of 600 or 1000 mg/kg 30 min before irradiation or treatment with cyclophosphamide (CY). DDC reduced the radiocurability of solitary leg tumors by a protective factor (PF) of 1.24, but it protected the same mice against radiation-induced hair loss and leg contractures more efficiently (PFs = 1.44 and 1.51), providing an appreciable therapeutic gain. Other experiments showed that artificial lung metastases were protected by a PF of only 1.1. DDC, however, was highly protective against radiation-induced hematopoietic tissue injury (PF = 1.59). DDC enhanced the antitumor effect of CY against artificial lung metastases. For example, CY (40 mg/kg) reduced the number of colonies from 69.0 +/- 7.3 in control mice to 16 +/- 5.8 when used alone, but it reduced to 4.5 +/- 1.3 when combined with DDC. It also augmented the CY efficacy against solitary FSA leg tumors. In the NFSA tumor system, in which CY alone enhanced spontaneous metastasis formation, DDC abolished this undesirable effect of CY. Experiments are in progress to determine whether DDC affects the damaging effect of CY on normal tissues.

370. DOSE AND INTERVAL RELATIONSHIP FOR THE INTERACTION OF WR-2721 AND NITROGEN MUSTARD WITH NORMAL AND MALIGNANT CELLS

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Department of Medicine, Wayne State University, Detroit, MI.
Int J Radiat Oncol Biol Phys; 10(9):1561-4 1984

The protective effect of WR-2721 on nitrogen mustard (HN2) cytotoxicity against hematopoietic stem cells as well as the potentiation effect previously noted against leukemia cells was further examined for dose and interval dependency for these opposite effects. For AKR leukemia cells, a dose dependent potentiation of HN2 cytotoxicity was noted with WR-2721. The magnitude of the potentiation was about 10-fold with 5 mg/mouse WR-2721 and nearly 100-fold at 10 mg/mouse. Interval studies showed maximum potentiation occurred when WR-2721 was given close in time to HN2 and decreased in magnitude as the interval between the agents increased. However, a pronounced potentiation of cytotoxicity was also found when HN2 followed WR-2721 by 4 to 12 hr. For hematopoietic stem cells, a protective effect of WR-2721 on HN2 cytotoxicity was observed. This effect decreased rapidly with interval between the agents with no protection noted for an interval of 6 hr. These results indicate that agents like WR-2721 may have an important therapeutic role in chemotherapy.

371. CHEMOPROTECTION OF VARIOUS NORMAL TISSUES BY WR-2721 (MEETING ABSTRACT)

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Proc Annu Meet Am Assoc Cancer Res; 25:324 1984

The radioprotective drug WR-2721 has also been proposed for preferential protection of normal tissues against chemotherapeutic drugs. We have investigated its protective action against cyclophosphamide (CY), cis-platinum (CDDP) and adriamycin (ADR) in the mouse. Injection of 400 mg/kg WR-2721 was given 30 min prior to chemotherapy. This treatment protected mice against the lethal effects of CY and CDDP (LD 50/30 assay) with protection factors (PF) of 1.25 and 2.5, respectively, but not against ADR (PF = 0.84). Studies of 3 tumors, fibrosarcomas, FSa and NFSa, and mammary carcinoma, MCaK, growing subcutaneously at an 8 mm size, showed negligible protection of CY induced growth delay by WR-2721, with PFs of 1.1, 1.03 and 0.97, respectively. This result indicated a favorable therapeutic ratio could be obtained with CY. In contrast to the large protection observed with the LD 50/30 assay, colon crypt cells were not protected from CDDP toxicity by WR-2721 (PF = 1.04). As was the case with animal survival, testicular stem cells were not protected against ADR cytotoxicity by WR-2721 (PF = 1.0). Furthermore, repeated injections of WR-2721 alone (5 and 10 daily injections of 300 mg/kg) produced significant killing of testicular stem cells and reduced sperm protection

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56 days later by 18% and 43%, respectively. Thus, although selective chemoprotection of normal tissue with WR-2721 may be possible, one must consider the specific drug used, the different normal tissues used as endpoints, and the possible cytotoxic effect of multiple doses of WR-2721.

372. **MODIFICATION OF WR 2721 OF THE RESPONSE TO CHEMOTHERAPY OF TUMOURS AND NORMAL TISSUES IN THE MOUSE**
Twentyman PR
Medical Res. Council Clinical Oncology, Hills Road, Cambridge, England
Br J Cancer; 47(1):57-63 1983

The sulfhydryl compound WR 2721 has been combined with a range of cytotoxic drugs in the mouse and the effects upon tumors and normal tissues determined. In the acute lethality (LD50/30) assay, mean protection factors produced by WR 2721 (200 or 400 mg/kg) were generally less than 1.3 for cyclophosp hamide (CTX), lomustine (CCNU) and chlorambucil (CHL) but a protection factor of 1.7 was obtained for cisplatinum (cis-P) in combination with 400 mg/kg of WR 2721. No protection against the depression of peripheral white cell count seen at 3 days after CTX, CCNU or cis-P was obtained with either 200 or 400 mg/kg of WR 2721. Significant protection of the RIF-1 sarcoma by WR 2721 against CTX and cis-P induced growth delay was seen. In the KHT sarcoma, WR 2721 produced small reductions in the growth delay caused by CCNU, melphalan and CHL but these were not statistically significant. These data show less differential normal tissue protection by WR 2721 than do a number of reports in the literature. (Author abstract) (13 Refs)

373. **EFFECT OF TUMOR SIZE ON S-2-(3-AMINOPROPYLAMINO)ETHYLPHOSPHOROTHIOIC ACID AND MISONIDAZOLE ALTERATION OF TUMOR RESPONSE TO CYCLOPHOSPHAMIDE**
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Department of Experimental Radiotherapy, University of Texas, M.D. Anderson Hospital and Tumor Institute, Houston.
Cancer Res; 43(7):3050-6 1983

The influence of tumor size on the ability of S-2-(3-aminopropylamino)ethylphosphorothioic acid (WR-2721) or misonidazole (MISO) to alter cyclophosphamide (CY) antitumor activity was investigated, using a chemically induced fibrosarcoma (FSA) and a spontaneous fibrosarcoma (NFSA) in C3Hf/Kam mice. Tumors were of two sizes at the time of treatment, 8-mm leg tumors and 4-day-old micrometastases in the lung. The antitumor activity of CY and its modification were assessed by growth delay of leg tumors and the reduction in the number of lung metastases. Both measures of tumor response were more pronounced as the dose of CY increased, and FSA was more sensitive to CY than was NFSA. WR-2721 (400 mg/kg), given 30 min before treatment with CY, reduced the effectiveness of CY on both FSA and NFSA. This reduction in effectiveness of CY was only minimal for leg tumors (dose-modifying factors were 1.1 for FSA and 1.03 for NFSA) but remarkable for lung micrometastases (dose-modifying factors were 1.81 for FSA and 1.55 for NFSA). Protection increased with the increase in the dose of WR-2721 and was also dependent on the time of injection relative to CY. The greatest protection occurred when WR-2721 was given within 30 min before to 15 min after CY. Tumor size had the opposite effect on MISO from that on WR-2721. MISO (1 mg/g) enhanced the effect of CY more effectively for leg tumors than for lung micrometastases: dose-modifying factors were 1.74 for FSA and 2.21 for NFSA growing in the leg and 1.27 for FSA and 1.11 for NFSA lung micrometastases. Therefore, tumor size appears to be a very important factor in determining the extent of WR-2721- and MISO-induced modification of CY antitumor effect.

374. **PROTECTION AND POTENTIATION OF NITROGEN MUSTARD CYTOTOXICITY BY WR-2721**
Valeriote F, Tolen S
Section Cancer Biology, Div. Radiation Oncology, Washington Univ. Sch. Medicine, 4511 Forest Park Blvd. Room 405, St. Louis, MO, 63108
Cancer Res; 42(11):4330-4331 1982

The radioprotective agent WR-2721 was examined for its effects on modifying the cytotoxicity of HN2 against normal and tumor cells in the AKR mouse. Quantitation was carried out by the spleen colony assay for both normal hematopoietic stem cells and AKR leukemia cells. Protection from drug toxicity and normal cell cytotoxicity was noted. Potentiation of cytotoxicity to AKR leukemia was found. (Author abstract) (15 Refs)

375. **THE EFFECT OF MISONIDAZOLE COMBINED WITH WR2721 ON TUMOUR RESPONSE AND LEUCOPENIA DUE TO CYCLOPHOSPHAMIDE OR MELPHALAN**
McNally NJ
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Br J Cancer; 46(4):670-674 1982

To increase the effectiveness of cyclophosphamide (CY) and melphalan (ME), each was combined with misonidazole (MISO) and WR2721 and therapeutic ratios determined for WHFIB tumors growing in inbred WHT/GyfBSVS mice. MISO was used in an attempt to increase the effectiveness of CY and ME through potentiation while WR2721 was used to reduce toxic effects of CY and ME on normal tissues. MISO enhanced the action of CY against the WHFIB tumor giving a dose-modifying factor (DMF) of approx 2. With ME, MISO gave a DMF of approx 2.4. WR2721 had no effect on the cytotoxicity of CY or ME or on MISO potentiation. MISO and WR2721, either alone or in combination, had no effect on tumor cell survival. Neither MISO nor WR2721, alone or together, had any effect on the WBC count nadir following 100 mg/kg CY or on the subsequent recovery of WBC. MISO and WR2721, either alone or in combination, had no effect on control mice or on the dose-effect curve for depression in WBC count at 3 days induced by CY. As with CY, MISO and WR2721, separately, had no effect on the WBC depression due to melphalan. The combination of 800 mg/kg MISO and 300 mg/kg WR2721 was moderately toxic to the mice. The results indicated that there is no benefit from the combination of WR2721 with MISO and CY or melphalan. WR2721 protected neither the tumor nor the normal tissue from the toxic action of the chemotherapeutic drugs and had no effect on the potentiation of their toxicity by MISO. (15 Refs)

376. **THE MODIFICATION OF MELPHALAN TOXICITY IN TUMOR BEARING MICE BY S-2-(3-AMINOPROPYLAMINO)-ETHYLPHOSPHOROTHIOIC ACID (WR2721)**
Millar JL, McElwain TJ, Clutterbuck RD, West EA
Dept. Physics, Inst. Cancer Res., Royal Cancer Hosp., Clifton Ave., Sutton, Surrey SM2 5PX, England
Am J Clin Oncol; 5(3):321-328 1982

The toxicity of melphalan in mice was reduced by the injection of S-2-(3-aminopropylamino)-ethylphosphorothioic acid (WR2721). This was seen in terms of reduced toxicity to the stem cells of the bone marrow and intestinal epithelium as well as improved animal survival. Using human melanoma xenografts and growth delay as an end-point, it was demon-

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strated that WR2721 did not protect this tumor from melphalan. With radiolabeled WR2721, it was shown that WR2721 was rapidly cleared from the blood and actively accumulated by all normal tissues except the CNS. Intact human tumor xenografts and Lewis lung tumors were less able to accumulate WR2721 than normal tissues, but in vitro studies showed that tissue fragments or single cell suspensions of tumors were as efficient as liver fragments or bone marrow cells in accumulating the drug. The rapid clearance of WR2721 and poor vascularity of the intact tumors were thought to be responsible for the differential uptake and protection of normal tissues by WR2721. (Author abstract) (16 Refs)

377. MODULATION OF CIS-PLATINUM RENAL TOXICITY BY THE RADIOPROTECTIVE AGENT WR 2721

Jordan SW, Yuhas JM, Glick J
Dept. Pathology, Univ. New Mexico Sch. Medicine, Albuquerque, NM, 87131
Exp Mol Pathol; 36(3):297-305, 1982

Pretreatment with the radioprotective thiol compound WR 2721 resulted in amelioration of renal histologic damage induced at 5 and 31 days in rats by a single exposure to cis-dichlorodiammineplatinum II (cis-Pt), an anticancer agent. Renal histopathologic changes 5 days after exposure consisted of tubular epithelial necrosis at the corticomedullary junction, while after longer time intervals, nuclear hypertrophy, anisonucleosis, and diminished tubular diameters were evident. The degree of histologic change at 5 days was inversely correlated with the amount of WR 2721 administered. At 31 days after a single cis-Pt dose following pretreatment with 200 mg/kg WR 2721, the dose reduction factor (treated/control) was 1.5-1.6. (Author abstract) (12 Refs)

378. PROTECTION AGAINST CIS-DICHLORODIAMMINE PT(II) CYTOTOXICITY IN VITRO BY CYSTEAMINE

Shrieve DC, Harris JW
Radiation Oncology Res. Lab., Dept. Radiation Oncology, Sch. Medicine, Univ. California, San Francisco, CA, 94143
Int J Radiat Oncol Biol Phys; 8(3/4):585-588, 1982

EMT6/SF mouse mammary tumor cells were exposed to cis-dichlorodiammine Pt(II) (DDP) for 1 hr in the presence of 10 milliM beta-mercaptoethylamine (MEA: cysteamine). MEA protected the cells against DDP when added simultaneously or when added after DDP was removed. As the time between exposure to DDP and MEA increased, the protective effect of MEA declined. Protection against DDP depended on the dose of MEA (max protection at 5 milliM), and, in the case of addition of MEA after DDP exposure, length of MEA exposure (max survival at 2 hr). (14 Refs)

379. ENHANCEMENT OF THE POTENTIATION OF RADIOTHERAPY BY PLATINUM DRUGS IN MOUSE TUMOR

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Radiobiology Lab., Norris Cotton Cancer Center, Mary Hitchcock Memorial Hosp., Hanover, NH, 03755
Int J Radiat Oncol Biol Phys; 8(3/4):501-503, 1982

Two ways to enhance potentiation of radiation therapy (RT) by cisplatin (CP) were studied in MTG-B mouse mammary carcinoma, implanted in the legs of female C3H mice. The first approach determined the efficiency of treatment sequencing and the second combined CP and RT with drugs that protect normal tissues from CP damage, thus allowing use of larger concentrations of CP. CP, diethyldithiocarbamate (DDTC), 5-thio-D-glucose (5-TG), and 5-2-(3 aminopropylamino)ethyl-phosphorothioic acid (WR-2721) were dissolved in normal saline and injected ip. Mice were anesthetized with pentobarbitol (60 mg/kg) 5 min prior to RT. X-irradiation was delivered locally to the tumor using a 2.0 cm diameter cone. The combination of CP and RT resulted in reduced TCD50 values with enhancement ratios greater than 1.3. Results suggested that greater potentiation occurred when CP was given 1 hr prior to RT compared to immediately following irradiation. CP 15 min before RT produced a more rapid tumor regression compared to CP injected immediately following RT. The addition of DDTC, WR-2721, or 5-TDG increased the CP LD50 values. Enhanced effects on the tumor occurred when 20 mg/kg CP and DDTC were combined with RT compared to tumor growth inhibition obtained with RT plus DDTC or CP plus DDTC. The marked effect on the radiation-derived TCD50 by CP administered prior to irradiation may be partly a result of a radiosensitization of hypoxic tumor cells by CP. (13 Refs)

380. WR-2721: ENHANCED CHEMOPROTECTION BY INCREASING CYCLOPHOSPHAMIDE ACTIVATION WITH PHENOBARBITAL

Glover DJ, Yuhas JM, Glick JH
Hematology-Oncology Section, Hosp. Univ. Pennsylvania, 3400 Spruce St., Philadelphia, PA, 19104
Int J Radiat Oncol Biol Phys; 8(3/4):571-574, 1982

A Fisher rat model was used to determine if WR-2721 protects against myelosuppression from cyclophosphamide (CY) by measuring daily WBC counts, if phenobarbital (PB) increases chemoprotection with WR-2721 and CY, and the effect of PB pretreatment on the clearance of WR-2721. It was shown that PB appears to enhance chemoprotection by WR-2721 against myelosuppression from CY by hastening marrow recovery and decreasing the extent of leukopenia. (17 Refs)

381. INFLUENCE OF WR 2721 ON THE EFFICACY OF RADIOTHERAPY AND CHEMOTHERAPY OF MURINE TUMORS

Clement JJ, Johnson RK
Experimental Therapeutics Section, Arthur D. Little, Inc., Cambridge, MA, 02140
Int J Radiat Oncol Biol Phys; 8(3/4):539-542, 1982

Influence of WR 2721 in combination with radiation (0-3,000 rad) or antitumor agents was evaluated and possible therapeutic benefits of WR 2721 were estimated by comparison with normal tissue protection data. Two solid tumors, M5076 and Lewis lung carcinoma (LLC) were injected as 1:10 tumor brei s into female C57Bl/6 x DBA/2 mice. The P388 lymphocytic leukemia ascites form was maintained ip in DBA/ 2 mice and was assayed in BALB/c x DBA/2 mice. WR 2721 at 500 mg/kg given 30 min prior to irradiation increased the survival curve (D0) values of ip P388 leukemia from 370 to 528 rad. WR 2721 also protected LLC from radiation. In general, WR 2721 reduced tumor regrowth delay at low radiation doses, and reduced tumor curability at higher radiation doses. WR 2721 protected mice against the toxic effects of cyclophosphamide (CYC) and melphalan (L-PAM). The LD50 for CYC and L-PAM in non-tumored mice was increased by 1.2 and 1.6 respectively, by pretreating mice with WR 2721 at doses of 300 or 500 mg/kg. The combination of 500 mg/kg WR 2721 with CYC against established M5076 tumor was no more effective than CYC alone at CYC doses of 210, 300, and 430 mg/kg. CYC at 614 mg/kg alone or in combination with WR 2721 was toxic. WR 2721 in combination with L-PAM was tested in early LLC and was found to be less toxic to tumor-bearing animals than L-PAM alone. WR 2721 protected systemic P388 leukemia from L-PAM at all L-PAM dose levels between 8.2-25 mg/kg. The therapeutic effectiveness of DNA binding agents in combination with WR 2721 was also evaluated in systemic P388 leukemia. At nontoxic levels the antitumor activity of etoposide and mi-

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toxantrone given ip was not significantly altered by co-administration of 500 mg/kg WR 2721 given sc or ip. The combinations were, however, markedly more toxic. (9 Refs)

382. DIFFERENTIAL PROTECTION AGAINST CYTOTOXIC CHEMOTHERAPEUTIC EFFECTS ON BONE MARROW CFUS BY WR-2721

Wasserman TH, Phillips TL, Ross G, Kane LJ
4511 Forest Park Blvd., Suite 311, St. Louis, MO, 63108
Cancer Clin Trials; 4(1):3-6 1981

The spleen colony assay was used to evaluate the ability of the radiation-protective agent WR-2721 to modify the cell killing of bone marrow by cytotoxic drugs. LAF1 mice were inoculated ip with WR-2721 (600 mg/kg) 0.5 hr prior to administration of cyclophosphamide, cis-platinum, 5-fluorouracil, nitrogen mustard, or carmustine. The cytotoxic drugs were given at 0.25-1.0 x the maximally tolerated dose (MTD) without WR-2721 and at 0.25-3.0 x MTD in combination with WR-2721. Two hr after administration of the cytotoxic drugs, the bone marrow from the femur was harvested and injected into recipients. The dose-modifying factor ranged from 1.5 for carmustine to 4.6 for nitrogen mustard. To test whether WR-2721 provides a differential protection of normal cells, BALB/c mice with transplanted EMT6/SF tumors were inoculated ip with WR-2721 (525 mg/kg); 0.5 hr later mice received iv injections of the same cytotoxic drugs. The tumor growth delay assay showed that WR-2721 did not affect the ability of cytotoxic drugs to inhibit the tumor regrowth. (13 Refs)

383. MODIFICATION OF TUMOUR AND HOST RESPONSE TO CYCLOPHOSPHAMIDE BY MISONIDAZOLE AND BY WR 2721

Twentyman PR
Medical Res. Council Clinical Oncology and Radiotherapeutics Unit, Hills Road, Cambridge, England
Br J Cancer; 43(6):745-755 1981

The effect has been studied of adding either misonidazole (MISO) or the radioprotective drug, WR2721, to cyclophosphamide (CY) treatment of mice bearing either the RIF-1 or KHT sarcomas. In RIF-1, the growth delay due to CY was increased by the addition of 1 mg/kg of MISO. At doses below 75 mg/kg of CY, the effect was dose modifying but, at higher doses, the curves were parallel. When the MISO dose was reduced to 0.33 mg/g, the effect was reduced but not entirely lost. Only a small enhancement of the CY response in the KHT tumor was seen with single doses, but the enhancement was greater with fractionated doses. The growth delay produced by CY in both tumor systems was reduced if WR 2721 (400 mg/kg) was given 30 min earlier. At a CY dose of 75-100 mg/kg the dose-modifying factor (DMF) was approx 0.7-0.8 but, at least in the RIF-1 tumor, was not so low at higher doses of CY. Determination of the LD50 for CY showed a DMF of approx 1.2-1.3 for MISO (0.33 mg/g) and approx 0.8 for WR2721 (400 mg/kg). Neither modifying agent appeared to cause any consistent change in the pattern of body-wt loss after CY, but WR 2721 reduced the myelosuppression seen at 3-4 days after CY. The data suggest that modification of tumor response to CY by the addition of MISO varies from tumor to tumor, and is very dependent upon the MISO dose. The protective effect of WR 2721 when combined with CY is not confined to normal tissues, and at a dose of 400 mg/kg may be as great in terms of tumor response as in terms of acute LD50 in this system. At a lower dose of WR 2721, however, some differential protection may occur. (Author abstract) (18 Refs)

384. TREATMENT OF TUMOURS WITH THE COMBINATION OF WR-2721 AND CIS-DICHLORODIAMMINEPLATINUM (II) OR CYCLOPHOSPHAMIDE

Yuhas JM, Speliman JM, Jordan SW, Pardini MC, Afzal SM, Culo F
Cancer Res. and Treatment Center, Univ. New Mexico, Albuquerque, NM, 87131
Br J Cancer; 42(4):574-585 1980

The ability of WR-2721 [S-2(3-aminopropylamino) ethylphosphorothioic acid] to selectively protect the host against the toxic effects of multiple doses of cis-dichlorodiammineplatinum [cis-Pt] or cyclophosphamide [CY] has been studied in mice and rats bearing three different tumors. Selective protection against cis-Pt induced nephrotoxicity has been demonstrated under all conditions studied, with the extent of protection being inversely related to the size of the cis-Pt dose. For example pre-treatment with 200 mg/kg of WR-2721 30 min before each weekly dose of 2 mg/kg of cis-Pt allows the administration of this cytotoxic agent for 3x longer before nephrotoxic injury. In none of these studies was there tumor protection. The same pattern was observed with CY, but quantitation of the extent of marrow protection was not possible for the multiple treatment studies, due to the longer latent p eriod between induced and observed death with this drug. We conclude, therefore, that for both of these drugs, selective protection of the kidney and marrow is not only maintained under conditions of multiple treatment, but actually enhanced due to the need for smaller doses of cytotoxic agents in these protocols. (Author abstract) (18 Refs)

385. SELECTIVE INHIBITION OF THE NEPHROTOXICITY OF CIS-DICHLORODIAMMINEPLATINUM(II) BY WR-2721 WITHOUT ALTERING ITS ANTITUMOR PROPERTIES

Yuhas JM, Culo F
Cancer Res. and Treatment Center, Univ. New Mexico, 900 Camino de Salud, NE, Albuquerque, NM, 87131
Cancer Treat Rep; 64(11):57-64 1980

Injection of 200 mg/kg of body wt of WR-2721 30 min before graded doses of cis-dichlorodiammineplatinum(II) (cisplatin) increased the resistance of Fischer 344 rats to cisplatin-induced nephrotoxicity by a factor of 1.7, but did not alter the sensitivity of three different transplanted tumors to cisplatin-induced growth delay. As a consequence, it was possible to administer doses of cisplatin which would have been lethal in the absence of WR-2721 injection, resulting in a proportionally greater tumor response. WR-2721 can, therefore, increase the effectiveness of cisplatin therapy through selective protection against the toxic side effects of chemotherapy. (Author abstract) (7 Refs)

386. A MORE GENERAL ROLE FOR WR-2721 IN CANCER THERAPY

Yuhas JM
Cancer Res. and Treatment Center, Univ. New Mexico, Albuquerque, NM, 87131
Br J Cancer; 41(5):832-834 1980

The possibility that S-2-(3-aminopropylamino) ethylphosphorothioic acid (WR-2721) could selectively protect normal tissues against the toxic interaction of radiation and alkylating agents was investigated in six groups of eight female Fischer 344 rats. 3M2N mammary carcinoma was transplanted into the right hind leg of each rat. Therapy was initiated when the tumors had grown to approx 9 mm. Rats were given an injection of saline or WR-2721, followed 30 min later by x-irradiation (0 or 2,500 rads) and/or cis-dichlorodiammineplа-

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tinum (Cis-Plat). Without WR-2721 pretreatment, radiation plus Cis-Plat showed greater than additive injury to the tumor and skin. With WR-2721 pretreatment (200 mg/kg), the toxic interaction with the skin was eradicated, while the toxicity to the tumor remained fully expressed. (9 Refs)

387. DIFFERENTIAL PROTECTION OF NORMAL AND MALIGNANT TISSUES AGAINST THE CYTOTOXIC EFFECTS OF MECHLORETHAMINE

Yuhas JM

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Cancer Treat Rep; 63(6):971-976 1979

The ability of the radioprotective drug S,2-(3-aminopropylamino)ethyl-phosphorothioic acid (WR-2721) to protect mice against mechlorethamine (HN2)-induced hematopoietic death and to protect sc transplanted Line 1 lung carcinoma against HN2-induced growth delay is reported. WR-2721 (400 mg/kg, ip) in jected 15 min before an iv injection of HN2 caused a 2x increase in the resistance of mice to hematopoietic death; the protection declined with a half-life of 1.5-2 hr. The HN2 LD50 in C57BL/6J mice was 5.25 mg/kg, while the LD50 for mice pretreated with WR-2721 was 10.90 mg/kg. HN2 was less effective (LD50 7.0 mg/kg) in delaying tumor growth in BALB/c mice pretreated with WR-2721 (350 mg/kg) compared with controls (LD50 3.2 mg/kg). When HN2 was given 30 or 60 min after WR-2721, no tumor protection was apparent, and a 2x increase in tumor growth delay was obtained without increased hematopoietic injury. (17 Refs)

B.

Adriamycin

388. INDICATION OF REDUCED DOXORUBICIN-INDUCED CARDIAC TOXICITY BY ADDITIONAL TREATMENT WITH ANTIOXIDATIVE SUBSTANCES

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Experientia; 39(1):62-64 1983

The influence of antioxidative substances on doxorubicin-induced cardiac toxicity was studied in C57BL mice. Tocopherol (500 mg/kg), glutathione (1,000 mg/kg), cysteamine (15 mg/kg) and L-cysteine (1,000 mg/kg), injected ip 24 hr before doxorubicin treatment (15 mg/kg ip) were able to reduce malonaldehyde production in cardiac tissues significantly. SH-containing substances with high reducing activity, such as vitamin E, could be a useful tool in clinical trials to prevent doxorubicin induced cardiac damage. (Author abstract) (13 Refs)

389. MECHANISM OF ADRIAMYCIN CARDIOTOXICITY: EVIDENCE FOR OXIDATIVE STRESS

Olson RD, Boerth RC, Gerber JG, Nies AS

Dept. Pediatrics, Vanderbilt Univ., Nashville, TN

Life Sci; 29(14):1393-1401 1981

Adriamycin is a widely used anticancer agent but the cumulative dose-dependent cardiotoxicity severely limits the use of adriamycin in the treatment of neoplastic diseases. Recent evidence suggests that adriamycin forms reactive free radical species which may oxidize cellular components and produce the cardiomyopathy. Sulfhydryl donors and antioxidants have been effective in preventing acute adriamycin cardiotoxicity in animal models presumably by scavenging the free radicals generated by adriamycin. The sulfhydryl donors, namely cysteamine and N-acetyl cysteine, do not interfere with adriamycin's antitumor activity. The results from these studies give considerable hope that the chronic cardiotoxicity from adriamycin may be attenuated in people, thereby giving additional therapeutic benefit from this antitumor agent. (Author abstract) (44 Refs)

390. REGULATORY ROLE OF GLUTATHIONE AND SOLUBLE SULFHYDRYL GROUPS IN THE TOXICITY OF ADRIAMYCIN

Olson RD, MacDonald JS, Van Boxtel CJ, Boerth RC, Harbison RD, Slonim AE, Freeman RW, Oates JA

Dept. Pharmacy, Vanderbilt Univ. Sch. Medicine, Nashville, TN

J Pharmacol Exp Ther; 215(2):450-454 1980

The effects of adriamycin (AM) on tissue levels of reduced glutathione (GSH), and the effects of sulfhydryl (SH) donors on these levels and AM-induced cardiac lesions and lethality were studied using male Swiss ICR-HA mice. GSH levels in the liver, RBC, and heart were significantly reduced by AM (15 mg/kg, ip). The GSH levels subsequently increased to control values in the RBC and to greater than control in liver and heart. Cysteamine (CA: 50 mg/kg, ip), an SH donor, prevented soluble SH levels from falling below control values after AM treatment. The lethality of AM, which was dose-related, was also greatly reduced by treatment with CA or N-acetyl cysteine (NAC). Prolonged treatment with the SH donors was not necessary to protect against AM lethality. The lethality of AM was potentiated by diethyl maleate-induced depletion of endogenous GSH. Administration of CA or NAC significantly diminished or protected against the myocardial damage induced by a single dose of AM. (22 Refs)

391. EFFECT OF SULFHYDRYL-CONTAINING COMPOUNDS ON THE ANTITUMOR EFFECTS OF ADRIAMYCIN

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Dept. Pharmacology, Pediatrics, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232

Toxicol Appl Pharmacol; 54(1):168-175 1980

The effects of cysteamine (CYS: 50 mg/kg, ip) and N-acetylcysteine (NAC: 100 mg/kg, ip) on the antitumor activity of adriamycin (ADR) were examined. The lifespan of male mice bearing a transplantable Ehrlich ascites carcinoma was significantly increased by ADR administered ip for 4 successive days at subletha! dosages of 1.5 or 2.5 mg1kg/day. The CYS or NAC was administered 1 hr before and 7 hr after the ADR treatment; neither inhibited the antitumor activity of the ADR, but actually increased the life spans of the tumor-bearing mice. When further experiments were performed in vitro to determine the effects of the sulfhydryl-containing compounds on the uptake of ADR in tumor cells, NAC did not affect the uptake of ADR at any of three concentrations tested, whereas the CYS, at a 10-fold excess of the ADR concentration, produced a small increase in the ADR uptake. ADR-induced inhibition of 3H-thymidine incorporation into DNA of tumor cells was found to be unaffected by CYS or NAC. The results of these studies indicated that concurrent administration of CYS or NAC which are agents known to decrease the cardiotoxicity of ADR does not decrease their antitumor effects. (17 Refs)

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REVIEWS

392. CHEMICAL MODIFIERS OF CANCER TREATMENT CONFERENCE ABSTRACTS

American College of Radiology

Chemical Modifiers of Cancer Treatment - Conference Abstracts. Brown, J.M. (Conference Chairman), American College of Radiology, 1985.

This volume contains author abstracts of presentations at a conference dealing with chemical modification of radiation and chemotherapy of cancer. Both enhancement of therapeutic index or inhibition o f toxic side effects are examined, in experimental systems in vivo and in vitro, and in the clinical setting. One session of the conference (Protection of Normal Tissues to Radiation and Chemotherapy) included pharmacokinetic studies with WR2721 in cancer patients and the use of this radioprotector to ameliorate the toxic effects of radiation, and of cis-platinum and cyclophosphamide toxicity during therapy. Experimental studies, in vivo and in vitro, reported on the role of radioprotectors both in protection against primary damage and in increasing DNA repair; mechanisms of action; pharmacokinetics; and protection of various organ systems against radiation damage.

393. ANTIRADIATION DRUGS. 1974-AUGUST, 1982 (CITATIONS FROM THE INTERNATIONAL AEROSPACE ABSTRACTS DATA BASE)

National Technical Information Service

Springfield, VA

Antiradiation Drugs. 1974-August, 1982 (Citations from the International Aerospace Abstracts Data Base). Available from National Technical Information Service, Springfield, VA, as PB82-872771:, 67 pp., 1982.

This bibliography contains citations concerning antiradiation drugs for radiation protection. The biological efficacy and the physiological effects of these drugs are discussed. Radiation protection for spacecraft crews are also discussed. (This updated bibliography contains 62 citations, 10 of which are new entries to the previous edition.) (Author abstract)

394. NEWER METHODS OF CANCER TREATMENT: RADIATION SENSITIZERS AND PROTECTORS

Phillips TL

Dept. of Radiation Oncology, Univ. of California, San Francisco, San Francisco, CA

Cancer - Principles and Practice of Oncology. 2nd Edition. DeVita VT Jr, Hellman S, Rosenberg SA, eds. Philadelphia, Lippincott, p. 2256-71, 1985.

Radiation sensitizers are discussed in terms of radiation effects at cellular and subcellular levels, development of hypoxic cell sensitizers, dose-response relationships, results of initial trials, new drug development, cytotoxicity, interaction with alkylating agents, and cytotoxic chemotherapy. At least four classes of agents can modify radiosensitivity and have the potential for differential sensitization, namely, hypoxic cell sensitizers, thiol-depleting agents, PLD-repair inhibitors, and pyrimidine analogues. Radiation protectors are discussed in terms of initial radiobiologic events, differential normal tissue protection, observed protective capacity in normal tissues, early clinical trials, future clinical trials, new drug development, and interaction with alkylating agent chemotherapy. Designations, chemical names, and structures are given for five different cysteamine-related thiophosphate radioprotective compounds. The repair of target molecule free radicals by reduction and their fixation by oxidation provide the potential for augmentation of the results of clinical radiotherapy. Pyrimidine analogues show considerable promise as radiation sensitizers in tumors of the br ain, sarcomas of soft tissue and bone, and other sites where differential uptake of alkylating agents could occur. The use of sulfhydryl-containing compounds to repair free radical lesions in the DNA of aerated normal tissues has proved possible. There appears to be a differential effect on normal tissue versus tumor through increased drug uptake of certain compounds in normal tissues compared to tumor and through the decreased protective efficacy of these compounds in hypoxic cells. Sulfhydryl-containing radioprotective compounds also protect cells against the toxic effects of alkylating agent chemotherapy. (74 Refs)

395. SENSITIZERS AND PROTECTORS IN RADIOTHERAPY

Brown JM

Department of Radiology, Stanford University Medical Center, CA 94305.

Cancer; 55(9 Suppl):2222-8 1985

The rationale for hypoxic cell radiosensitizers, of which misonidazole (MISO) is the most widely used drug, is based on the premise that hypoxic cells limit the cure rate of tumors to conventional radiotherapy. There is evidence that this is the case for tumors of the head and neck and possibly also for carcinoma of the cervix and lung. Despite numerous trials, however, MISO has not shown a significant clinical benefit. However, it can be demonstrated that little or no effect would have been expected at the doses of MISO used. New and more efficient radiosensitizers are now available which are more likely to produce significant improvements in local control with radiotherapy. The sulfhydryl radioprotector WR-2721 protects normal more than malignant tissues in animals from damage by radiation and chemotherapy agents. Evidence for protection of bone marrow and kidney has now been obtained for cyclophosphamide and cisplatin, respectively, in Phase I clinical trials. Sensitizers and protectors demonstrate that chemical modification of the therapeutic index is possible for both radiation and chemotherapy treatment of cancer. (45 Refs)

396. PHARMACOLOGY OF DMSO

Jacob SW, Herschler R

Department of Surgery, Oregon Health Sciences University, Portland 97201.

Cryobiology; 23(1):14-27 1986

A wide range of primary pharmacological actions of dimethyl sulfoxide (DMSO) has been documented in laboratory studies: membrane penetration, membrane transport, effects on connective tissue, anti-inflammation, nerve blockade (analgesia), bacteriostasis, diuresis, enhancement or reduction of the effectiveness of other drugs, cholinesterase inhibition, nonspecific enhancement of resistance to infection, vasodilation, muscle relaxation, antagonism to platelet aggregation, and influence on serum cholesterol in experimental hypercholesterolemia. This substance induces differentiation and function of leukemic and other malignant cells. DMSO also has prophylactic radioprotective properties and cryoprotective actions. It protects against ischemic injury. (115 Refs)

397. THE ROLE OF ENDOGENOUS THIOLS IN INTRINSIC RADIOPROTECTION

Revesz L

Int J Radiat Biol; 47(4):361-368 1985

Observations are reviewed from experiments performed to study the role of endogenous thiols in the radiation response of cells using a glutathione-deficient and a related glutathione-proficient cell strain. The effect of glutathione in the initial radical reactions was considered and the yield of single-

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strand DNA breaks was the end-point of the response. The rejoining of breaks and clonogenic survival were chosen as end-points when, in addition, the role of glutathione in the subsequent biochemical processes was studied. The results were interpreted to indicate that glutathione plays a role in both the radical and the biochemical reactions which follow irradiation. In the former case it functions as a damage-restituting reactant, in general agreement with the 'competition model'. Some biochemical repair processes, in particular those concerned with the rejoining of breaks induced by radiation in the presence of oxygen or misoniazole, appear also to be critically dependent on glutathione. Due, probably, to its particular spatial distribution, endogenous glutathione is specific in the radical processes, and exogenous thiols cannot be substituted for it. No such specificity was indicated in the biochemical processes related to strand break rejoining.

398. STUDIES ON RADIOPROTECTORS IN MAMMALS AND THEIR POSSIBLE USE IN RADIOTHERAPY - A SUMMARY (37 Refs)

Kumar S

Radiobiol Radiother (Berl); 26(3):359-65 1985

Keywords (MeSH): Amino Acids, Sulfur/*therapeutic use; Animal; Drug Combinations/therapeutic use; Ethiofos/*therapeutic use; Human; Mercaptopropionylglycine/*therapeutic use; Mice; Neoplasms/radiotherapy; Organothiophosphorus Compounds/*therapeutic use; Plant Extracts/*therapeutic use; Radiation Injuries, Experimental/prevention and control; Radiation-Protective Agents/*therapeutic use; Radiotherapy/adverse effects; Review.

399. THE INDUCTION AND CONTROL OF RADIOGENIC TRANSFORMATION IN VITRO: CELLULAR AND MOLECULAR MECHANISMS (212 Refs)

Borek C

Department of Radiology, Columbia University College of Physicians and Surgeons, New York, NY 10032.

Pharmacol Ther; 27(1):99-142 1985

Keywords (MeSH): Animal; Antineoplastic Agents/toxicity; Antipain/pharmacodynamics; Benzamides/pharmacodynamics; Calcium/metabolism; Carcinogens/toxicity; Cell Line; Cell Membrane/metabolism; Cell Transformation, Neoplastic/*radiation effects; Cells, Cultured; Chromosomes/radiation effects; Cocarcinogenesis; DNA/radiation effects; Female; Free Radicals; Human; Neoplasms, Radiation-Induced/familial and genetic/pathology; Oncogenes; Phenotype; Pregnancy; Radiation-Protective Agents/pharmacodynamics; Review; Transfection.

400. CHEMICAL MODIFIERS OF CANCER TREATMENT

Phillips TL

Department of Radiation Oncology, University of California, San Francisco.

Int J Radiat Oncol Biol Phys; 10(9):1791-4 1984

It is clear that the investigators involved in chemical modification have reached an historical turning point in radiobiology. Studies in the 1960s concentrated on physical and chemical radiobiology, studying dose response relationships and initial chemical reactions. More recently, the area of biochemical radiobiology has been entered and studies of cellular modification of the initial events and cellular repair mechanisms have been initiated. The future would appear to belong to biochemical modulation. The ability to increase or decrease the various cellular components through enzyme blocking or stimulation gives much greater power to our abilities to chemically modify radiation and cytotoxic agents in the future. We are thus come from the winding country lane of sensitizer development to the complex city expressway of chemical modification. Non-nitro-compounds and pyrimidine analogs have entered the field, and cellular biochemistry has assumed a major role in our future progress. Although misonidazole has overall been a clinical failure, the investment in its laboratory and clinical study has opened up a whole new field of chemical modification based on sound biochemical principles.

401. PROMISE OF RADIOSENSITIZERS AND RADIOPROTECTORS IN THE TREATMENT OF HUMAN CANCER

Phillips TL, Wasserman TH

Department of Radiation Oncology, University of California - San Francisco.

Cancer Treat Rep; 68(1):291-302 1984

Over the past 30 years, as an understanding of radiation chemistry has developed, it has been possible to develop compounds which modify the initial radiochemical event. In addition, certain physiologic means such as hyperbaric oxygen or blood flow restriction have also been developed as methods to modify radiation response through the radiochemical processes. Following the success of certain hyperbaric trials, a great effort was made to develop chemical agents which would mimic oxygen in their sensitization of hypoxic cells. A large series of compounds have now been identified with such properties and several of these have entered clinical trial. The first compound to receive widespread testing, misonidazole, has proven too toxic to be used in adequate doses for clinically relevant sensitization. Two new nitroimidazole analogs, which are excluded from the central nervous system, promise to allow much higher degrees of sensitization in planned clinical trials and new non-nitro drugs are under development. Radioprotection can be achieved through various methods, including restriction in blood flow and the use of sulfhydryl-containing compounds which again modify the initial radiochemical events. To be successful in tumor therapy, such agents must be selective in protecting the normal tissues. One class of compounds, the thiophosphates, show differential protection of normal tiss ue vis-a-vis tumor through several mechanisms. After extensive animal testing, one of these compounds, WR 2721, is now in phase I clinical testing, with phase II evaluation planned for the near future. Other potential sensitizers with varying degrees of differential activity in tumor versus normal tissue are also discussed.

402. CHEMICAL MODIFIERS OF RADIATION AND CHEMOTHERAPY: TUMOR SENSITIZATION AND NORMAL TISSUE PROTECTION

Coleman CN, Wasserman TH

Div. of Radiation Therapy and Medical Oncology, Stanford Univ. Sch. of Medicine, Stanford, CA

Cancer Treat Res; 22:141-68 1984

The subject matter of this article is introduced by consideration of the following topics: clinical rationale for radiosensitizers and protectors, radioresistance of tumors, oxygen effect, reoxygenation, radioprotectors, and hyperbaric oxygen. These topics are followed by discussions of clinical trials of radiosensitizers, radioprotectors, nitroimidazoles as chemosensitizers, and thiol and other agents as protectors. Completed and continuing Phase II and Phase III trials of misonidazole (MISO) as a radiosensitizer for treatment of patients (pts) with head and neck cancer have provided no definitive proof of the ability of MISO to alter the local control rate of tumors achievable with radiation. SR-2508 had been predicted to be a less neurotoxic drug than MISO or desmethylmisonidazole (DMM); DMM was predicted to be of intermediate toxicity. Although DMM could be delivered at about 1.5 times the MISO dose before neurotoxicity became

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limiting, lack of clinical value caused cessation of the trials. Phase I clinical trials have recently been initiated with SR-2508. WR-2721, a thiol-containing radioprotector in which the thiol group is covered by a phosphate group to reduce toxicity, also has recently been entered in Phase I clinical trials, and drugs like MISO are being tested as chemosensitizers. It was hoped that such agents would enhance the effectiveness of chemotherapeutic drugs by various mechanisms, but the most likely effect appears to be direct cell killing during a period of tumor hypoxia; when observed in vitro, this is known as the 'pre-incubation effect.' The radioprotector WR-2721 is currently undergoing Phase I trials as a chemoprotector against such agents as cisplatin, cyclophosphamide, and nitrogen mustard; early results do not show any chemoprotective value, but completion of the trials will be required to obtain a firm answer. (80 Refs)

403. MODIFICATION OF RADIATION RESPONSE

Suit HD
Department of Radiation Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.
Int J Radiat Oncol Biol Phys; 10(11):101-8 1984

Response modifiers have been defined and several examples of modification of response of tissues of laboratory animals or of theoretical models were presented. I have reviewed several efforts to asses s the clinical value of serveral of the radiation response modifiers and described some major problems. A major and quantitatively undefined problem for clinical testing of response modifiers is the heterogeneity of clinical material. An area of laboratory and clinical investigation which has large potential is examination for indicators of response probability so as to identify individual patients who are likely to benefit by application of particular radiation response modifiers. There is a need for clinical trials to determine if the results of Henk and associates can be verified. Had Henk been able to publish such results in 1962 instead of 1977, it is virtually certain there would have been considerable effort to verify his results and to investigate numerous other sites. Further, there would have been greater stimulus to the laboratory to provide means to stratify patients according to evidence of hypoxic regions or failure to reoxygenate. Also efforts would have been made to increase the efficacy of hyperbaric oxygen, e.g., suppression of oxygen utilization. The disappointing results from studies with misonidazole should not discourage the testing of new sensitizers of hypoxic cells provided they can be administered at drug doses which achieve substantially higher ER values. New trials of the pyrimidine analogs against tumor which are surrounded by slowly or non-dividing normal tissue appear appropriate. Emphasis was placed on the practical clinical value of radiation protectors which can be applied topically or administered regionally. (22 Refs)

404. SYNTHETIC ANTIOXIDANTS: BIOCHEMICAL ACTIONS AND INTERFERENCE WITH RADIATION, TOXIC COMPOUNDS, CHEMICAL MUTAGENS AND CHEMICAL CARCINOGENS

Kahl R
Department of Pharmacology, University of Mainz, F.R.G.
Toxicology; 33(3-4):185-228 1984

Biological actions of 4 commonly used synthetic antioxidants butylated hydroxyanisole, butylated hydroxytoluene, ethoxyquin and propyl gallate - on the molecular, cellular and organ level are compiled. Such actions may be divided into modulation of growth, macromolecule synthesis and differentiation, modulation of immune response, interference with oxygen activation and miscellaneous. Moreover, an overview of beneficial and adverse interactions of these antioxidants with exogenous noxae is given. Beneficial interactions include radioprotection, protection against acute toxicity of chemicals, antimutagenic activity and antitumorigenic action. Possible mechanisms of the antitumorigenic action of antioxidants are discussed. This discussion is centered around antioxidant properties which may contribute to a modulation of initiation-related events, especially their ability to interfere with carcinogen metabolism. The beneficial interactions of antioxidants with physical and chemical noxae are contrasted to those leading to unfavorable effects. These include radiosensitization, increased toxicity of other chemicals, increased mutagen activity and increased tumor yield from chemical carcinogens. At present, the latter one can most adequately be characterized as tumor promotion at least in the case of butylated hydroxytoluene. It is concluded that current information is insufficient to promote expectations as to the use of antioxidants in the prevention of human cancer. (367 Refs)

405. RADIOSENSITIZERS AND PROTECTORS

Nori D, Kim JH, Hilaris BS, Chu F
Department of Radiation Therapy/Brachytherapy Service, Memorial Sloan-Kettering Cancer Center, New York, New York.
Cancer Invest; 2(4):321-30 1984

Keywords (MeSH): Animal; Antineoplastic Agents, Combined/therapeutic use; Clinical Trials; Human; Metronidazole/therapeutic use; Misonidazole/therapeutic use; Neoplasms/radiotherapy; Oxygen; Pyrimidines/therapeutic use; Radiation-Protective Agents/*therapeutic use; Radiation-Sensitizing Agents/*therapeutic use; Ethiofos/therapeutic use.

406. THE BIOCHEMISTRY OF HYPOXIC CELLS

Jacobson EA
The University of Western Ontario, London, Ontario, Canada
Diss Abstr Int kBl; 43(8):2526-B 1983

Cells in tumors that are more than 150 microns from blood vessels become hypoxic and are nearly three times more resistant to ionizing radiation as cells that are well oxygenated. Initially cells from V79-171b multicell spheroids were separated using isopycnic or pseudoisokinetic density gradients of Percoll; only one population of cells was identified using either method. V79 cells were then grown as monolayer cultures under conditions of controlled oxygen tension and culture density. Three oxygen tensions were used: normal aerobic (2.1 x 10(5) ppm O2); moderate hypoxia (2 x 10(3) ppm O2) where some growth inhibition and complete radioprotection occurred; extreme hypoxia (less than 10 ppm O2) where there was complete growth inhibition and radioprotection. Electron micrographs showed a decrease in mitochondrial number and an increase in mitochondrial size and lipid vacuoles following exposure to extreme anoxia. When cultures made extremely hypoxic were returned to normal oxygen tensions, mitochondrial size rapdily returned to normal while lipid continued to accumulate in vacuoles for a further 6 hours. Mitochondrial and lipid vacuole size increased slightly under conditions of intermediate oxygen tensions. The radiosensitizing chemical, misonidazole (1 mM), prevented the increase in mitochondrial size during exposure to extreme hypoxia. Significant increases in the incorporation of 3H-palmitate and 14C-acetate were observed into triglycerides, cholesterol, cholesterol esters, free fatty acid, and phosphatidylcholine lipid fractions obtained from cultures exposed to extreme hypoxia. (no Refs)

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407. MODIFICATION OF THE RADIATION EFFECTS FOR OVERCOMING RADIATION-RESISTANT HYPOXIC TUMOR TISSUE (104 Refs)

Moldenhauer H, Rose H, Saul G, Wolf G, Kehrberg G
Radiobiol Radiother (Berl); 24(5):597-614 1983

Keywords (MeSH): Animal; Central Nervous System Diseases/chemically induced; Dogs; English Abstract; Human; Hyperthermia, Induced; In Vitro; Intestines/radiation effects; Lymphocytes/drug effects; Metronidazole/therapeutic use; Mice; Misonidazole/therapeutic use; Neoplasms/radiotherapy; Neoplasms, Experimental/metabolism/*radiotherapy; Nerve Tissue/drug effects/radiation effects; Nitro Compounds/therapeutic use; Oxygen/metabolism; Radiation Dosage; Radiation-Protective Agents/therapeutic use; Radiation-Sensitizing Agents/adverse effects/toxicity/*therapeutic use; Rats; Review; Ethiofos/therapeutic use.

408. NEWER METHODS OF CANCER TREATMENT: SECTION 3. RADIATION SENSITIZERS AND PROTECTORS

Phillips TL
Dept. Radiation Oncology, Univ. California, San Francisco, San Francisco, CA
Cancer - Principles and Practice of Oncology. DeVita VT, Hellman S, and Rosenberg SA, ed. Philadelphia, Lippincott, 1926 pp., 1982.

Sensitizers are discussed in relation to: radiation effects at the cellular and subcellular level, development of hypoxic cell sensitizers, sensitizer dose-response relationships, initial clinical trials with misonidazole, current clinical trials, new drug development, cytotoxicity, and interaction with other cytotoxic chemotherapy. Protectors are discussed in relation to: initial radiobiologic events, differential normal tissue protection, observed protective capacity in normal tissues, early clinical testing, new drug development, and interaction with alkylating agent chemotherapy. The identification of the basic mechanisms involved in radiation killing of cells through the understanding of radiation chemistry and radiation biology has allowed for the clarification of a number of modifying mechanisms. The repair of target molecule free radicals by reduction and their fixation by oxidation provides the potential for augmentation of the results of clinical radiotherapy. A wide range of compounds have been discovered which exhibit electron affinity and which can mimic oxygen in their ability to sensitize the hypoxic cells to tumor radiation. There is suggestive evidence that these compounds may differentially sensitize tumor to alkylating chemotherapy as well. It has been demonstrated recently that radioprotective compounds are also active in protecting cells against toxic effects of alkylating agent chemotherapy. (51 Refs)

409. PIONS, PROTECTORS. EXAMPLES OF A VIGOROUS DECADE IN RADIOTHERAPY

Kligerman MM
Hosp. of the Univ. Pennsylvania, 3400 Spruce St., Box 322, Philadelphia, PA, 19104
Am J Clin Oncol; 5(2):101-113 1982

Results of pion radiation therapy (PRT), radiation protection, and pretreatment before use of alkylating agents are discussed. In 98 of 112 evaluated patients treated with PRT, the tumor site was head , neck, prostate, brain, or pancreas. Relation of acute to late effects with variation in dose are tabulated. All patients were treated with pions and had been observed for 12 mo or more. Two severe late reactions were observed in the group of patients. The use of chemical modifiers in radiation therapy is also of interest. A protector WR2721 was given 15-20 min before radiation treatment or the iv administration of the alkylating agent. The principal toxic effects of the protector that have been observed clinically are hypotensiveness, hypertensiveness, emesis, and somnolence. The most important toxic manifestation, observed in varying degrees in 11 patients, was a decrease in the systolic blood pressure. Pretreatment in connection with the use of alkylating agents was studied in 14 patients given 450 mg/square meter WR2721 before alkylating agents. Seven received the protector before cytoxan, the other seven before cis-platinum. In some patients minimal, partial, or complete tumor response occurred, tending to confirm laboratory studies that predicted that tumor tissues could not be protected by WR2721. (45 Refs)

410. PROBLEMS AND PROSPECTS OF DEVELOPMENT OF CLINICAL RADIOBIOLOGY

Konoplyannikov AG
Res. Inst. Medical Radiology, Obninsk, USSR
Med Radiol (Mosk); 27(9):46-53 1982

Current research in the field of clinical radiobiology is reviewed with special emphasis on the analysis of radiation effects on the cellular and molecular levels, and on the analysis of the effects of various radiomodifying agents. The differences in the rate of repair of sublethal injuries in the bone marrow and in the intestinal mucosa were found to cause a clear-cut dose interval between the bone marrow and intestinal variants of radiation sickness after gamma irradiation. Application of such radiomodifying agents as electron-seeking compounds, microwave hyperthermia, hypoxia, and radiation-protectors was shown to provide a selective increase of the radiosensitivity of tumor cells. (49 Refs)

411. CURRENT ROLE OF NITROIMIDAZOLE SENSITIZERS AND SULFHYDRYL PROTECTORS IN CLINICAL ONCOLOGY

Coleman CN, Brown JM
Div. Radiation Therapy, Stanford Univ. Medical Center, Stanford, CA
Appl Radiol; 11(4):31-32,37-38,42-43 1982

The rationale for development of radio- and chemosensitizers and radioprotectors and current clinical applications of these compounds are discussed. The therapeutic effect of radiotherapy (RT) or chemotherapy (CT) generally increases with increasing doses of therapy. The maximum dose is limited by the toxic effects on normal tissues. With the use of these compounds, by increasing the sensitivity of tumor cells, protecting normal cells, or both, the effective dose of therapy can be increased. Misonidazole was the first 2-nitroimidazole to enter clinical trials as a tumor sensitizer. Doses of the drug are limited by neural toxicity, indicated primarily by sensory peripheral neuropathy. In Phase 2 trials the incidence of neuropathy was 27% and was related to total dose rather than the administration schedule. The maximum therapeutic dose of misonidazole is 10.5-12.0 g/square meter. Efforts to reduce toxicity are aimed at producing drugs that are less lipophilic and more hydrophilic. SR-2508 is currently being tested in animals. Desmethylmisonidazole is undergoing Phase 1 clinical trials. Sulfhydryl compounds protect normal tissues from the effects of ionizing radiation by scavenging free radicals created by the radiation. WR-2721 is being tested in Phase 1 trials. Animal studies indicate that this drug protects bone marrow, skin, salivary glands, and the gastrointestinal tract, but not the brain and spinal cord. WR-2721 is apparently also effective against the toxic effects of some CT agents. (37 Refs)

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412. POTENTIALS AND LIMITATIONS OF BIOCHEMICAL RADIATION PROTECTION

Fickweiler E
Liebigstr. 21, DDR-7010 Leipzig, E. Germany
Dermatol Monatsschr; 168(11):721-725 1982

The use of radiation protectors during various forms of radiation therapy is discussed. The use of topical agents is limited by high toxicity and imperfect pharmacokinetics. Agents that have been useful include low-mol-wt thiols, antioxidants, dimethylsulfoxide, thymine, and beta-carotene. Protective agents act by producing anoxia to reduce formation of free radicals, neutralization of free radicals, or protection of sensitive sites on the DNA molecule. (3 Refs)

413. BIOCHEMICAL MECHANISM OF RADIOPROTECTIVE ACTION OF ADENYL COMPOUNDS

Koshcmeenko NN
No affiliation given
Biol Nauki; (2):5-18 1982

Literature data on the biochemical substrate of the radioprotective action of adenyl nucleotides (adenosine, adenine, and mixtures and complexes of adenylates with other radioprotective agents) are reviewed. The metabolism of the adenyl compounds, the hypotheses on their biologically active forms, and the hormone-like effect of adenosine are discussed. Adenosine may be bound to the adenylate cyclase receptors. (107 Refs)

414. TIME-SCALE AND NATURE OF RADIATION-BIOLOGICAL DAMAGE: APPROACHES TO RADIATION PROTECTION AND POST-IRRADIATION THERAPY

Singh A, Singh H
Medical Biophysics Branch, Whiteshell Nuclear Res Establishment, Atomic Energy Canada Ltd. Res. Co., Pinawa, Manitoba ROE 1LO, Canada
Prog Biophys Mol Biol; 39(2):69-107 1982

Time-scale and effects of energy deposition by high energy radiation applied to biological systems are reviewed, and the consequences of DNA, protein, cellular, mitotic, and carcinogenic damage are discussed. The nature of DNA repair and the roles of hydroxyl radicals, superoxide anions, and singlet oxygen in inducing biological damage are reviewed. Radiation protection and post-irradiation therapy are discussed at the biochemical level. (400 Refs)

415. ACCOMPLISHMENTS PROBLEMS AND PROSPECTS: A CONFERENCE SUMMARY

Adams GE
Physics Div., Inst. Cancer Res., Clifton Ave., Sutton, Surrey, England
Int J Radiat Oncol Biol Phys; 8(3/4):805-808 1982

The main problems of the conference on radiotherapy (1981 yr) are highlighted including tasks accomplished, problems resolved since the First Key Biscayne Conference, and future prospects. Topics discussed include clinical studies and the benefit of misonidazole in radiotherapy, mechanisms of chemosensitization, new radiosensitizers, improvements in sensitizing efficiency, radio-protective drugs, cytotoxicity and chemosensitization, and mechanisms of chemosensitization. Implications of the new rapid developments in chemosensitization are emphasized. (no Refs)

416. SENSITIZERS AND PROTECTORS IN CLINICAL ONCOLOGY

Phillips TL
Dept. Radiation Oncology, Univ. California, M-330, San Francisco, CA, 94143
Semin Oncol; 8(1):65-82 1981

Misonidazole (MNZ; Ro 07-0582) has been given several clinical trials as a radiosensitizer. MNZ therapy can enhance clinical responses to radiotherapy (RT) in patients with Grade III-IV malignant gliomas and cancers of the lung, head/neck, and cervix. However, the beneficial effects of MNZ seem to be small at the doses now deliverable (12 g/square meter over 6 wk). Delivery of up to 10x as much radiosensitizer would be required to obtain an enhancement ratio of 2-3 with every RT fraction over a 6-wk course. Neurotoxicity is the dose-limiting factor for MNZ. It may be possible to modify the chemical structures of MNZ analogs so as to dissociate neurotoxicity from electron affinity. MNZ seems to sensitize tumors to alkylating agents, but it also alters the pharmacology of these agents and may enhance their toxicities to normal tissues. The differential effects of S-2-(3-aminopropylamino)ethyl phosphorothioic acid hydrate (WR-2721) and other sulfhydryl group-containing radioprotective agents seem to involve increased uptakes of the agent in normal tissues and a lower protective efficacy in hypoxic tumor cells. WR-2721 protects the bone marrow, skin, mucous membranes, salivary glands, and small intestine against RT; it has less radioprotective activity in the lung and kidney, and does not protect the CNS. Clinical trials of WR-2721 in patients receiving RT for head/neck or abdominal cancer and in patients receiving whole-body or hemibody RT are planned. This agent seems to protect against only the alkylating activity of alkylating agents. Clinical trials of combinations of WR-2721 with cyclophosphamide, melphalan, nitrogen mustard, and cis-diamminedichloroplatinum(II) are recommended. (52 Refs)

417. THE POTENTIAL FOR RADIATION SENSITIZERS AND RADIATION PROTECTOR COMBINED WITH RADIATION THERAPY IN GYNECOLOGIC CANCER

Brady LW, Phillips TL, Wasserman TH
Dept. Radiation Therapy and Nuclear Medicine, Hahnemann Medical Coll. and Hosp. Philadelphia, 230 N. Broad St., Philadelphia, PA
Cancer; 48(2,Suppl):650-657 1981

Radiation sensitizers are agents which can increase the lethal properties of ionizing radiation when administered in conjunction with radiation therapy. They increase radiosensitivity without being innately toxic and give rise to significant increase in the radiation sensitivity of neoplasm over normal tissues. Much laboratory work, mostly in vitro, have shown that many chemical compounds can act as radiation sensitizers. The practicality depends upon the exploitation of the differences between normal and malignant cells when radiation sensitizers are used. Many tumors contain hypoxic cells which are relatively resistant to the lethal effects of ionizing radiation. In human tumors, these hypoxic cells present a potential barrier to successful treatment. The application of chemical radiosensitizers active against hypoxic cells offers great potential for improvement in cancer management using radiation therapy. Data is presented to illustrate the usefulness of these agents in gynecologic cancer. (Author abstract) (37 Refs)

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418. THEORETICAL BASIS FOR THE USE OF CERTAIN MODIFYING AGENTS IN THE RADIOTHERAPY OF MALIGNANT NEOPLASMS ('MODIFIER' PROGRAM)

Kuzin AM, Tsyb AF, Iarmonenko SP, Pelevina II, Konopliannikov AG

Inst. Biological Physics, Pushchino, USSR

Radiobiologiia; 21(5):744-751 1981

Results of the All-Union interinstitutional 'Modifier' Program are reported. The program included research in the field of theoretical radiobiology and clinical applications of radiosensitizing and radioprotective agents. Evaluation of the selective enhancement of radiation injury of hypoxic cells showed that electron acceptor compounds (EAC) had greater radiosensitizing effects than hyperbaric oxygen. Major disadvantages of EAC were CNS and gastrointestinal toxicity and ineffectiveness during split-course radiotherapy. Local hyperthermia was found to inhibit the postradiation repair and thus to enhance the efficacy of radiotherapy. Radioprotective agents or hypoxic gas mixtures were shown to provide a selective protection of normal tissues during tumor irradiation. (44 Refs)

419. BIOLOGICAL CHARACTERISTICS OF SOME IMPROVED RADIOPROTECTORS

Davidson DE, Grenan MM, Sweeney TR

Div. Experimental Therapeutics, Walter Reed Army Inst. Res., Washington, DC

Radiation Sensitizers: Their Use in the Clinical Management of Cancer. Brady LW, ed. New York, Masson Publishing USA, Inc., Cancer Management, Vol. 5, 521 pp., 1980.

Radioprotective characteristics of compounds developed by the United States Army Medical Research and Development Command Antiradiation Drug Development Program are reported. The most effective radioprotective compound is the phosphorothioate WR 2721. Radioprotective ability of WR 2721 is compared with that of delta,beta-aminoethylisothiouronium bromide hydrobromide and 2-mercaptoethylamine hydroc hloride. Radioprotective activities of WR 2529, WR 3689, WR 44923, WR 77913, and WR 16863 are described. (14 Refs)

420. ON THE POTENTIAL APPLICATION OF RADIOPROTECTIVE DRUGS IN SOLID TUMOR RADIOTHERAPY.

Yuhas JM

Cancer Res. and Treatment Center, Univ. New Mexico, Albuquerque, NM

Radiation-Drug Interactions in the Treatment of Cancer. Sokol GH, Maickel RP, ed. New York, John Wiley and Sons, Wiley Series in Diagnostic and Therapeutic Radiology, 325 pp., 1980.

The use of drugs that preferentially protect normal tissues from radiation injury is reviewed with emphasis on data accumulated on WR-2721, the most effective radioprotectant yet developed. There are two clinical situations where the combined use of radioprotective drugs and radiation may be beneficial: solid tumors where a cure is seldom obtained because of high tumor resistance (lung cancer), and solid tumors where the morbidity associated with conventional therapy is high. For the latter, conventional fractionation schemes could be used, with the end point being the extent of the reduction of morbidity. Initial clinical studies should be done with tumor sites with a relatively high incidence of acceptable complications. One good candidate for initial studies would be head and neck tumors in which the incidences of xerostomia and other buccal complications are high. WR-2721 tends to concentrate in the salivary glands and offers excellent protection to them. (74 Refs)

421. THE ROLE OF WR-2721 IN RADIOTHERAPY AND/OR CHEMOTHERAPY

Yuhas JM, Spellman JM, Culo F

Cancer Res. and Treatment Center, 900 Camino de Salud, N.E., Albuquerque, NM, 87131

Cancer Clin Trials; 3(3):211-216 1980

The present status of the proposed use of S-2-(3-aminopropylamino)-ethylphosphorothioic acid (WR-2721) in radiotherapy and/or chemotherapy is summarized. Previous studies have demonstrated an increased resistance to radiation of normal tissues (except CNS tissue) by injection of mice with 67% of the max tolerated dose of WR-2721, while no increase in resistance was observed in tumor tissue. In general, solid tumors are not radioprotected by WR-2721. It has been subsequently shown that normal tissues (except the brain and spinal cord) actively concentrate WR-2721, while solid tumors passively absorb it. The deficient vascularity of the tumors place them at a competitive disadvantage, in that the normal tissues remove the drug from the serum before the tumor can absorb it. In addition, the normal tissues (except CNS tissue) possess a temperature-dependent active concentration mechanism for WR-2721. The possibility of selective normal tissue protection against alkylating agents is also suggested. (19 Refs)

422. RADIATION SENSITIZERS. THEIR USE IN THE CLINICAL MANAGEMENT OF CANCER

Brady LW

Habneman Medical Coll. and Hosp., Philadelphia, PA

Radiation Sensitizers: Their Use in the Clinical Management of Cancer. Brady LW, ed. New York, Masson Publishing USA, Inc., Cancer Management, Vol. 5, 521 pp., 1980.

Proceedings of the Conference on Combined Modality Cancer Treatment: Radiation Sensitizers and Protectors are presented. Fourteen chapters on drug development, including discussions of nitroimidazoles, nitroheterocyles, misonidazole (MIS), time factors and radiosensitization, pharmacokinetics and radiosensitizing agents, allopurinols, and the development of hypoxic cell radiosensitizers are presented. In vitro drug testing is discussed in 14 chapters; topic considered include the effects of MIS and combinations of MIS with metronidazole, platinum complexes, nitrogen mustard, adriamycin, or carmustine on cell systems. In the fifteen chapters on in vivo testing, the effects and pharmacokinetics of MIS are considered along with interactions of MIS with other agents. The combination of radioprotective and radiosensitizing agents is considered. Radiation protectors, such as razoxane, WR-2721, and WR-1065, are discussed in seven chapters. Clinical trials of sensitizers are described in 11 chapters. Poster session discussions are presented. (1568 Refs)

423. RADIOBIOLOGICAL ROLE AND POSSIBILITIES OF SUPEROXIDE DISMUTASE (REVIEW)

Gusev VA, Brusov OS, Panchenko LF

All-Union Res. Inst. Clinical, Experimental Surgery, Moscow, USSR

Vopr Med Khim; 26(3):291-301 1980

Literature pertaining to the radiobiological significance of superoxide dismutase (SODM) and the role of its substrate in the processes of radiation injuries of the cell are reviewed. Administration of SODM before and after irradiation provided a marked protective effect (the factor of dose reduction was 1.56). The radioprotective effect of exogenous SODM might be associated with the ability of enzyme to preclude the damage of external cellular membranes. Radiosensitivity of bone marrow cells was correlated with the level of endogenous SODM. Pharmacological preparations of SODM (Orgotein) can be used for treatment of side-effects of radiotherapy in patients with tumors of the urinary bladder. (77 Refs)

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424. RATIONALE FOR INITIAL CLINICAL TRIALS AND FUTURE DEVELOPMENT OF RADIOPROTECTORS

Phillips TL
Dept. Radiation Oncology, Univ. California, M-330, San Francisco, CA, 94143
Cancer Clin Trials; 3(2):165-173 1979

The introduction of sulfhydryl radiosensitizers, particularly the thiophosphates, into clinical trials is reviewed. Topics considered include basic factors in differential radioprotection, protective efficacy in critical normal tissues, radioprotection during fractionated radiotherapy, tumor effects, pharmacologic data, toxic reactions, design of Phase I trials, design of Phase II trials, and design of Phase III trials. Although a few tumors seem to show similar protection to that of a range of normal tissues, most seem to show decreased protection as compared to normal tissue. It is possible to classify normal tissues in humans in terms of their limiting effect on radiotherapy doses. No information is available to date as to the degree of protection which might be seen in human tumors. Pharmacologic information from humans is also nonexistent at this point, and information on acute and chronic toxicity is limited. Phase I trials of radioprotective compounds are essentially similar to those for any other new pharmacologic agent. Each Phase II study will be relatively complex as compared to Phase II cytotoxic drug or even radiation sensitizer studies. Phase III studies will compare patients at a particular site with an elevated radiation dose schedule to patients given a similar radiation course at conventional radiation doses without drug administration. (25 Refs)

425. RESEARCH PLAN OF THE RADIOSENSITIZERS/ RADIOPROTECTORS WORKING GROUP OF THE RADIATION ONCOLOGY RESEARCH PROGRAM

Phillips TL, Yuhas JM, Adams GE, Brown JM, Chapman JD, Cory MJ, Johnson RJ, Johnston TP, Kinnamon K, Penta JS, Schwade JG, Stone HB, Urtasun RC, Utley JF, Lee WW, Wood H
Univ. California, San Francisco, CA
Int J Radiat Oncol Biol Phys; 5(5):651-676 1979

Planning efforts by the Radiation Oncology Coordination Subcommittee to establish a Radiation Oncology Research Program are described, the research logic is summarized, and progress and long range plans for research in radiosensitizers and radioprotectors are discussed. In the area of drug development, the discussion covers structures already synthesized, new analogues and types of radiosensitizers and radioprotectors, development of standard in vitro screening techniques, and research recommendations. A discussion of animal testing of radiosensitizers and radioprotectors includes the following topics: evaluation of newly identified hypoxic cell sensitizers; screening of compounds for radiosensitization in tumors in vivo; screening for radioprotection in a range of normal tissues; development of in vivo systems for testing newly identified compounds, and research recommendations. Three phases of clinical studies are outlined, and recommendations are made for approaches to clinical research. Specific proposals are summarized. (38 Refs)

426. RADIATION DAMAGE AND THE INTERFERON SYSTEM

Lvovsky E, Baze WB, Hilmas DE, Levy HB
Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20014
Tex Rep Biol Med; 35:388-393 1978

Data relating the interferon system to resistance to ionizing radiation were reviewed and analyzed. The data indicate that protection from low doses of ionizing radiation which leads to 'bone marrow syndrome' could be obtained by the prophylactic use of unrelated compounds, which include aminothiols, vasoactive amines, endotoxin, poly inosine (I)-poly cytosine (C), RNAase resistant-poly IC-poly lysine, and tilorone. Many of the radioprotective compounds studied also showed the ability to induce interferon and stimulate the development of a virus-resistant state. Aminothiols produced an interferon response in vitro and in vivo in mice which was neutralized by antibodies to mouse interferon. No direct relation between the amount of induced interferon and the extent of the radiation protection was observed. The most powerful chemical protectors, the aminothiols, had a dose reduction factor (DRF) of 2 and induced significantly less interferon than poly IC-poly lysine which had a DRF of 1.3. These results suggest that the mechanism of radiation protection may involve factors in addition to or other than interferon which play a role not only in the direct protection at the time of radiation, but also in the recovery from the damage. Possible mechanisms for the action of interferon and other radioprotective agents are discussed. (21 Refs)

427. CHEMICAL MODIFICATION OF RADIATION EFFECTS

Phillips TL
Cancer; 39(2 Suppl):987-998 1977

A number of powerful chemical compounds that modify radiation effects have been discovered over the past 25 years. There are four major classes of compounds: aminothiol radio-protectors which act on well vascularized euoxic cells and concentrate in tissues such as skin, gut and marrow; nitromidazole radiosensitizers which act on hypoxic tumor cells; pyrimidine analogues which are incorporated into the DNA of cycling cells and cause radiosensitization; and cancer chemotherapy agents which, in addition to their ability to kill tumor cells directly, also may sensitize tumor and normal cells to radiation. The mechanism of action, experimental activity, and clinical results or the potential for each of these agents are reviewed.

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This index is constucted from the National Library of Medicine's Medical Subject Headings (MeSH) which are associated with each abstract included in this publication. These MeSH terms can be used to retrieve similar information from the National Cancer Institute's online database CANCERLINE. The asterisk indicates that the concept indexed is a major point of the article. Bold-faced numbers refer to abstracts which are not indexed with a more specific related term and which may represent articles which are rather more general than the rest. For example: "Carcinogens....2, 17, 39"; where abstracts numbers 2 and 17 would be indexed to a more specific concept under "Carcinogens", such as "Benzo(a)pyrene", but abstract 39 would be indexed only to the level of detail of "Carcinogens".

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